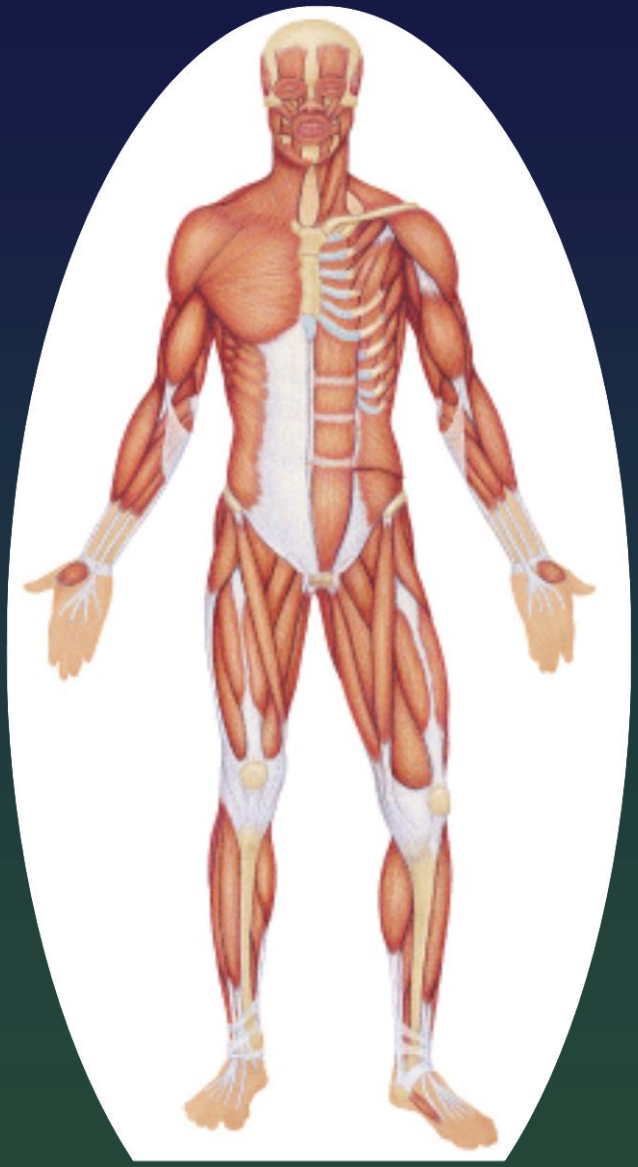

بسم الله الرحمن الرحيم

POLYMYOSITIS & DERMATOMYOSITIS



By

Dr. Abdelmoaty Afifi, MD

Chieh of Rehab, KAH.

POLYMYOSITIS–DERMATOMYOSITIS

Definition

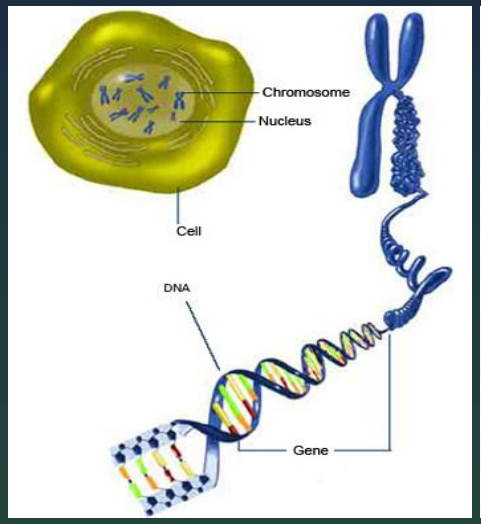
- Heterogeneous group of autoimmune Syndromes characterized by:
  - Ms. weakness with nonsuppurative inflammation in ms. tissue.
  - Unknown cause (idiopathic)
  - Systemic complications
- Myo = muscle; -itis = inflammation

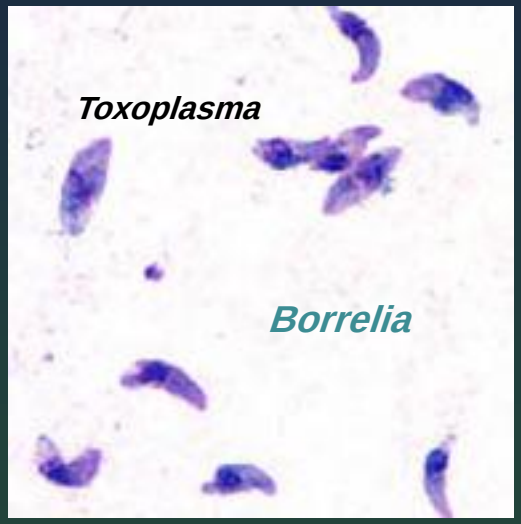
Major causes of Myopathy

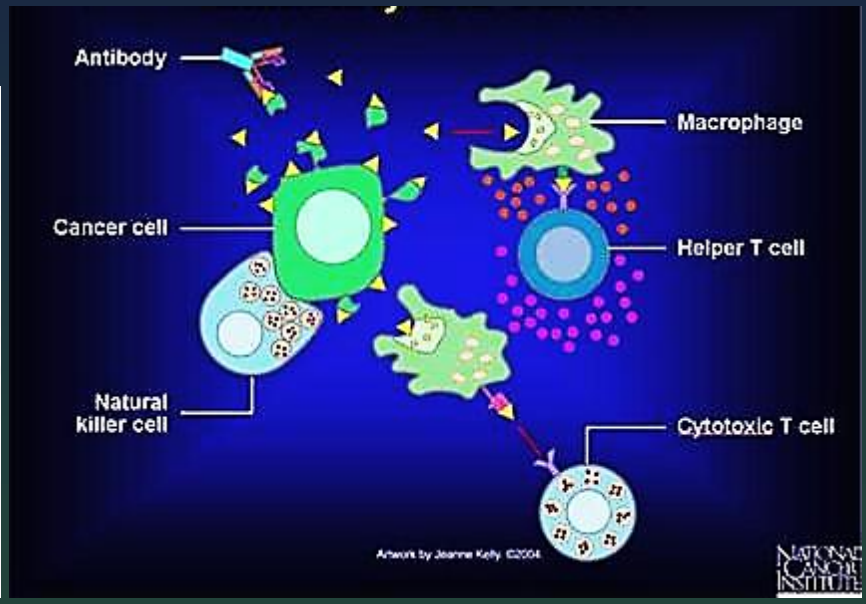
Neurological disorders Amyotrophic lateral sclerosis Myasthenia gravis Muscular dystrophies	**Infections** **Viral:** influenza, parovirus, Coxsacki, HCV, HBV CMV, HIV, Epstein Barr virus **Bacterial:** pyomyositis, Lyme disease **Fungal** **Parasitic:** Trichnosis, toxoplasmosis
Other rheumatic disorders RA, SLE, SS, PMR	
Electrolytes disturbances Hypokalemia Hypophosphatemia Hypocalemia Hypo- or hypernatremia	**Drugs and toxins** Cocaine, heroin, alcohol Corticosteroids Statins Colchicine, antimalarial, penicillamine
Endocrine disorders Hypothyroidism Cushing's syndrome Addison's disease	**Rhabomyolysis** Crush trauma, ms. ischemia Seizures, CVA Exertion
Metabolic disorders Mitochondrial myopathies Glycogen storage disease Disorders of lipids & purine metabolism	**Miscellaneous** Nutritional disorders (malabsorption, ↓vit D & E MI, critical illness Organ failure (uremia, liver failure) Carcinomatous neuromyopathy

ETIOLOGY

- Unknown?
- Combination of:







Genetic Predisposition (association with HLA DR3 and DRw52). DRB1*0301-DQA1*0501

Environmental trigger (Streptococci, influenza *Borrelia, Toxoplasma*, and Coxsackie virus)

Immune system susceptibility

Pathogenesis

- Damage to cell-mediated autoimmunity.
- Evidence: the cells invading the Ms. are 1/3 macrophages & 2/3 lymphocytes (predominantly cytotoxic/suppressor, occasionally helper)

Epidemiology

- Rare with annual incidence of 5-10 cases/million
- Prevalence of 50-90 cases/million
- Age of onset: “Bimodal” incidence peaks: 10-15 yrs
  35-55 yrs
- Female : male = 2-3:1. In childhood ♀:♂ =1:1
  In CTDs ♀:♂ = 8-10:1
- Race: African-American: whites = 3-4 : 1 in U.S,

CLASSIFICATION OF POLYMYOSITIS–DERMATOMYOSITIS

1) Grp I: Primary adult Idiopathic PM (35%)
2) Grp II: Primary adult Idiopathic DM
3) Grp III: DM or PM associated with neoplasia (1/10)
4) Grp IV: Childhood DM or PM associated w/ vasculitis
5) Grp V: PM or DM with associated CTD (1/3).
6) Inclusion body myositis (IBM): 16% - 28%

However, there are many other types of myositis that are much more uncommon

Idiopathic Inflammatory Myopathy

- Other forms of inflammatory myopathy:
  - Eosinophilic myositis
  - Myositis ossificans
  - Focal or localized myositis
  - Giant cell myositis
- Myopathies caused by infections
- Myopathies caused by drugs and toxins

GROUP I:
PRIMARY IDIOPATHIC PM

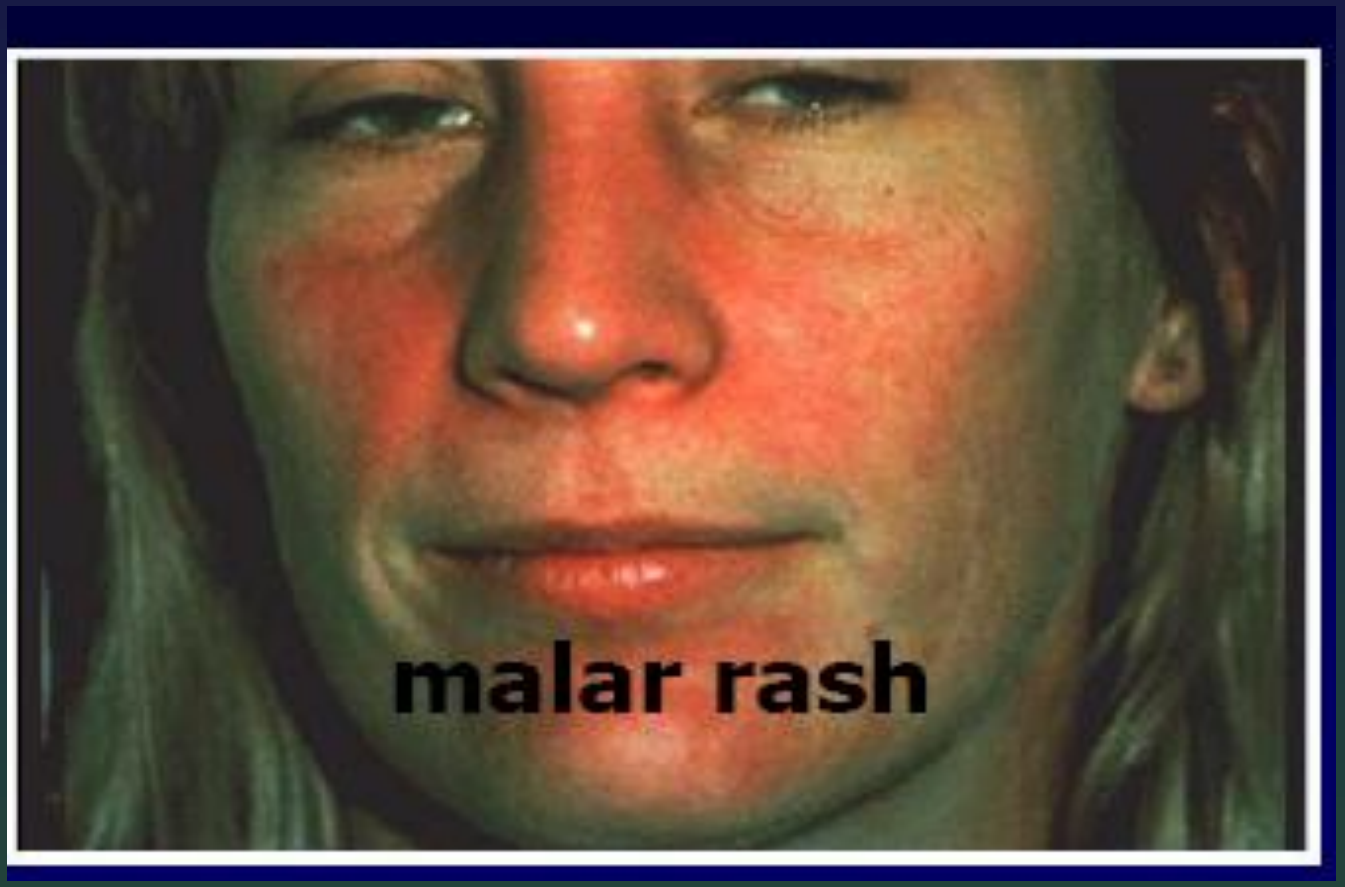
- Symmetrical weakness of the limb girdle ms and anterior neck flexors, progressing over wks or months with or without dysphagia (10% to 30%), dysphonia or respiratory ms involvement (more severe disease).
- Insidious onset over 3-6 months but rarely acutely over a few days
- Distal ms are spared in 75%.
- Ocular ms almost never affected.
- Minimal ms. pain and tenderness in 25-50%

Difficulty getting up from chairs, climbing stairs or lifting above the shoulders.

GROUP II:
PRIMARY IDIOPATHIC DM

- The skin lesions may precede or follow the ms syndrome
- Amyotrophic DM: skin manifestations in absence of clinically significant ms involvement.

Can be associated with malignancy (antedate or postdate DM by 2 yrs.). May develop extramuscular manifestations such as rapidly progressive interstitial lung disease even

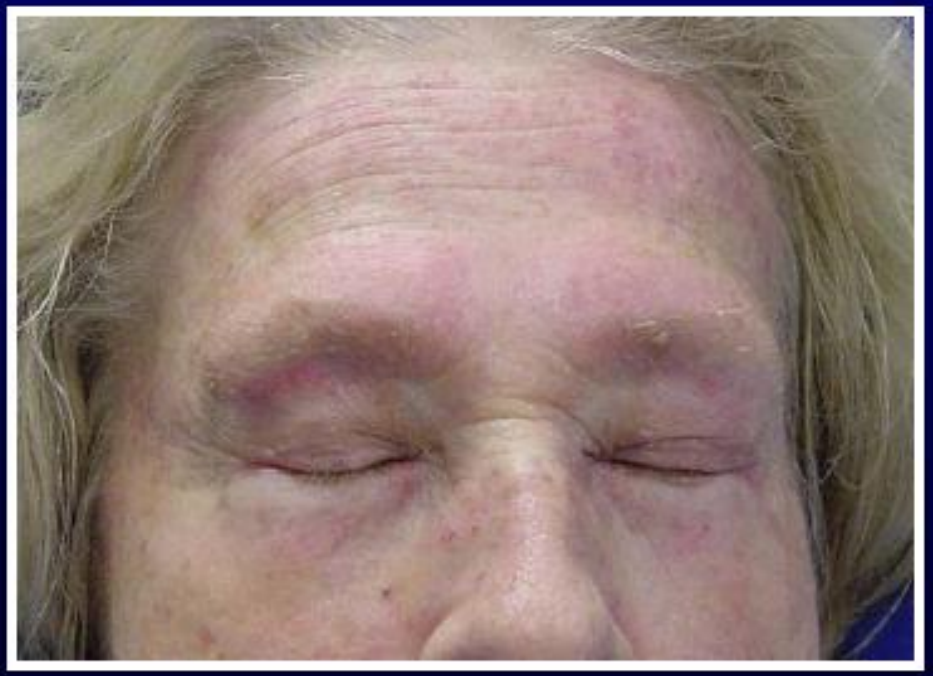


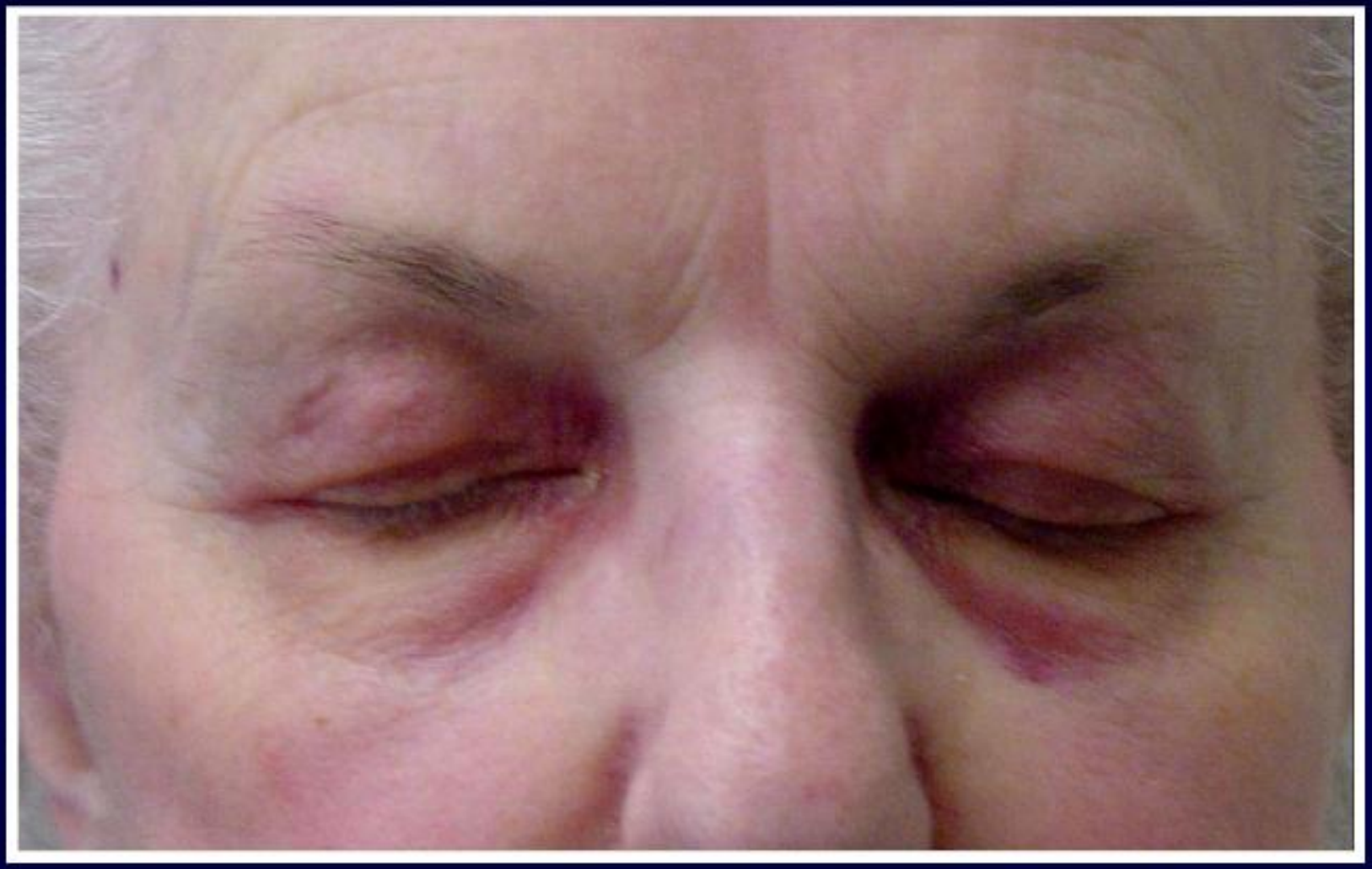
Heliotrope (lilac-colored) **rash**: purple to erythematous rash affecting the eyelids, malar region, forehead, and nasolabial folds. (Eyelids and nasolabial folds are typically spared in the rash of SLE).

Rashes of Dermatomyositis

Heliotrope Rash

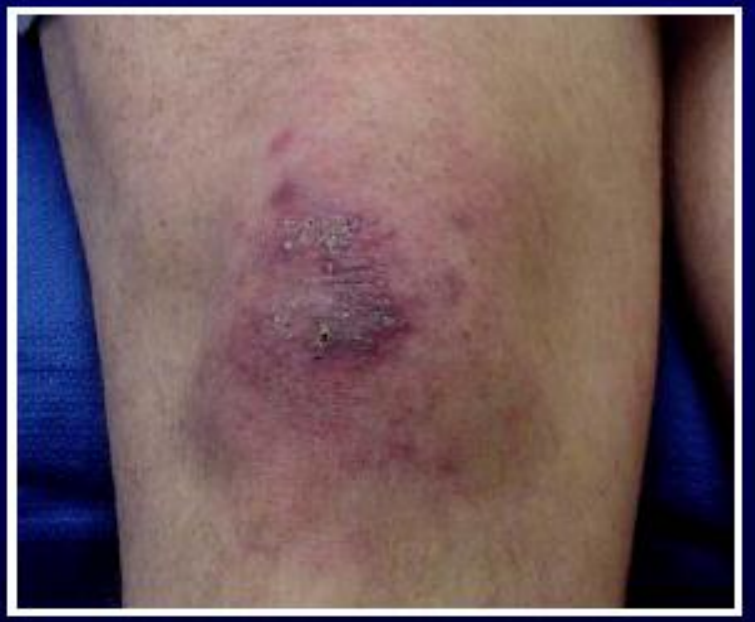
Reddish violaceous eruption
on upper eyelids +/- oedema





Heliotrope Rash

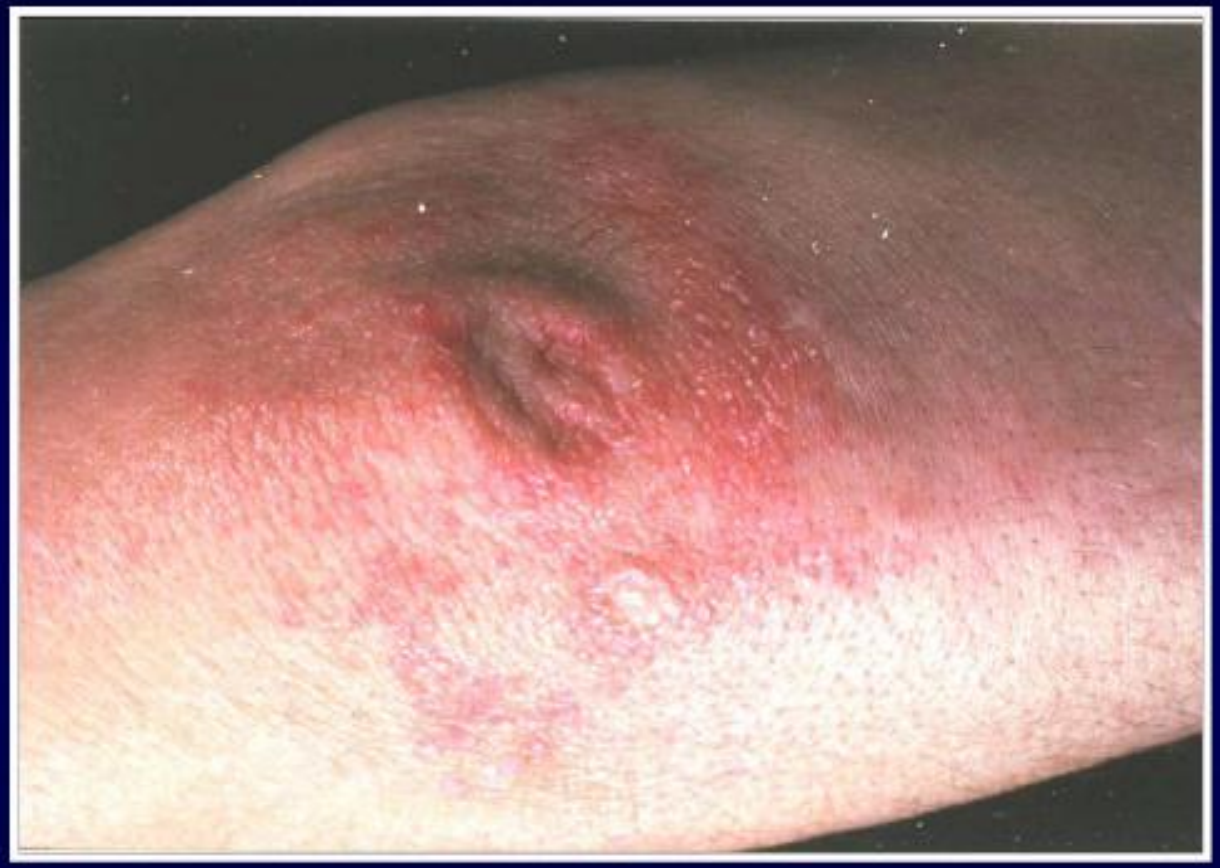
Rashes of Dermatomyositis



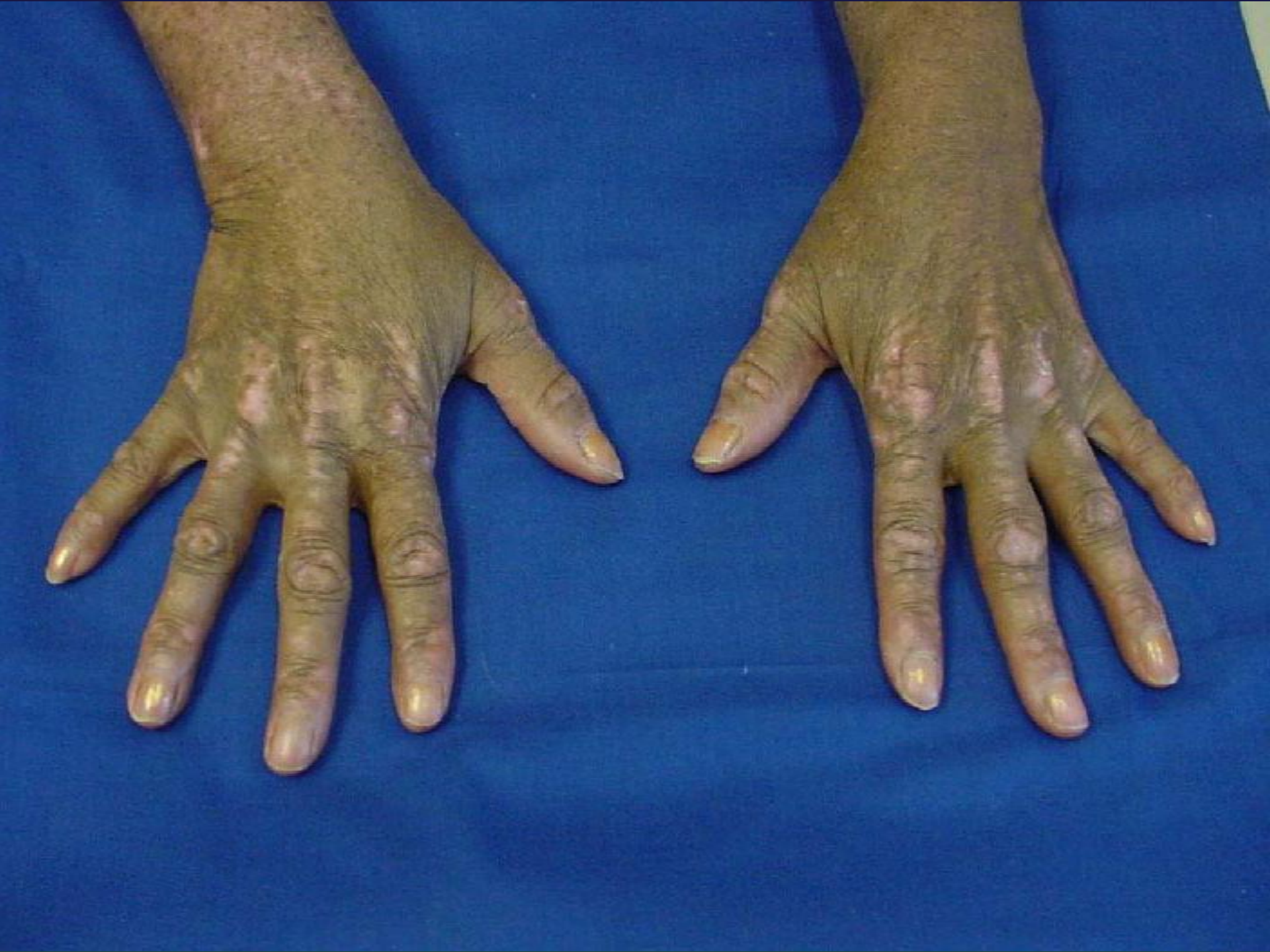
Gottron's Papules

symmetric violaceous erythematous eruption over knuckles

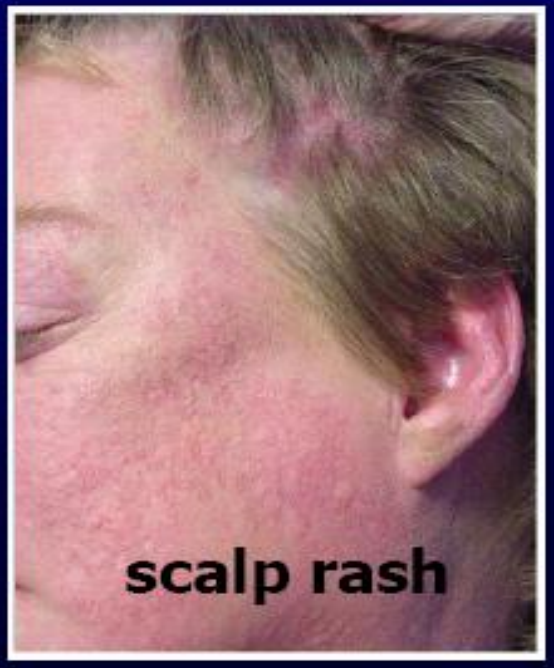
Rashes of Dermatomyositis

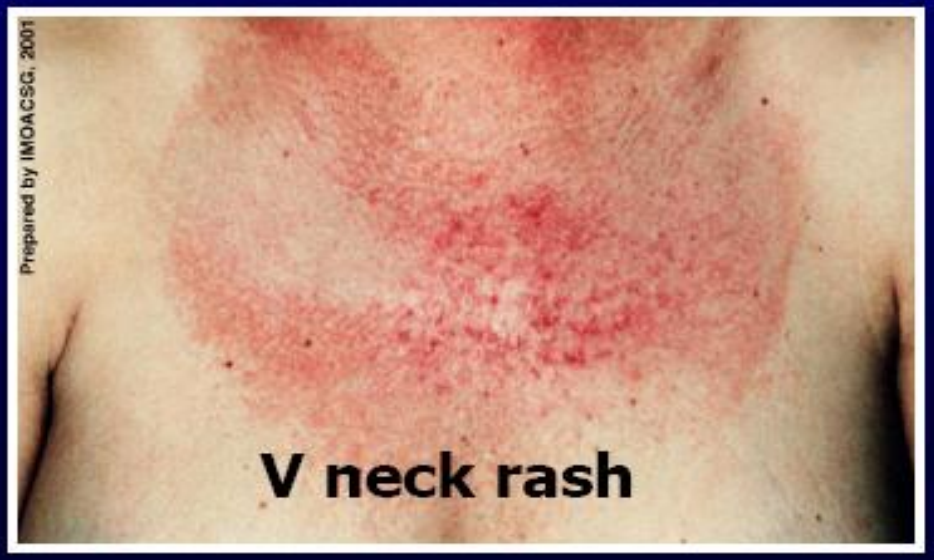


Gottron's sign



Other Rashes of Dermatomyositis

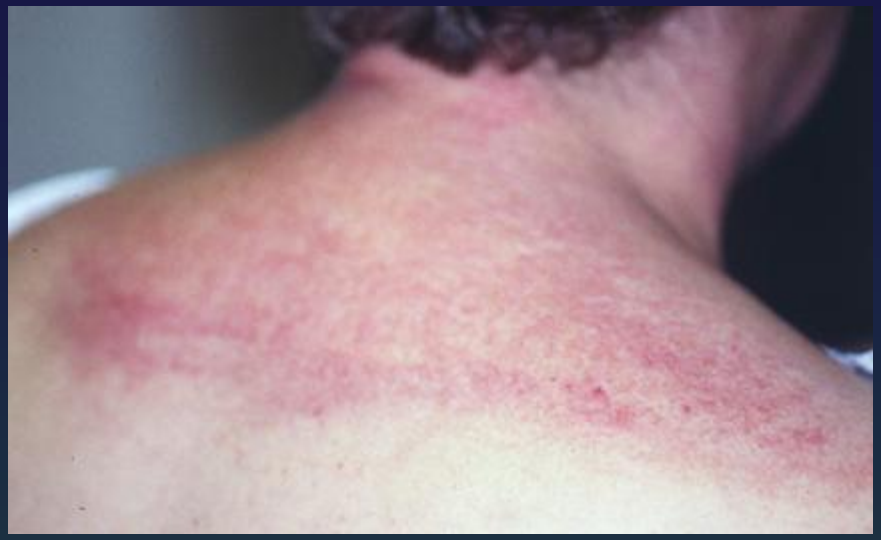




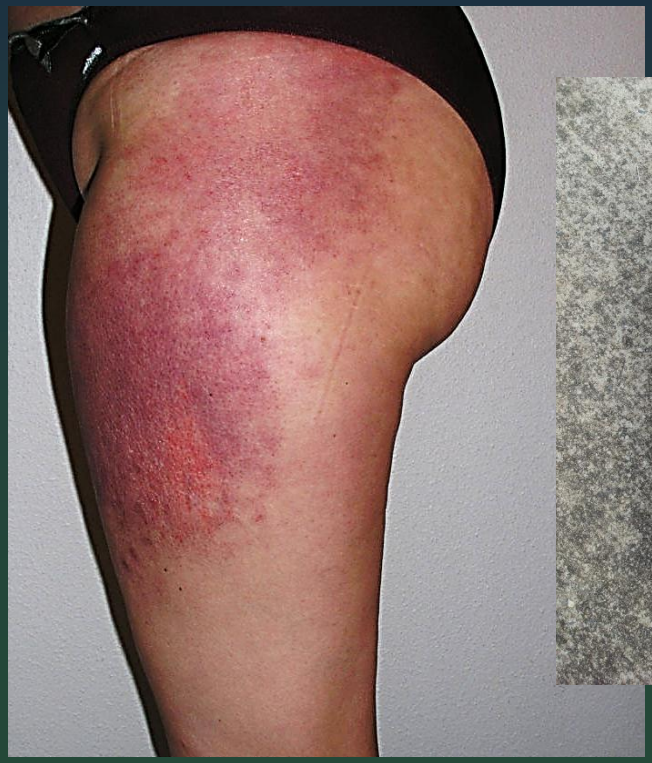
Diffuse/localized erythema over chest, neck, or over forehead, chin, malar area

Shawl sign

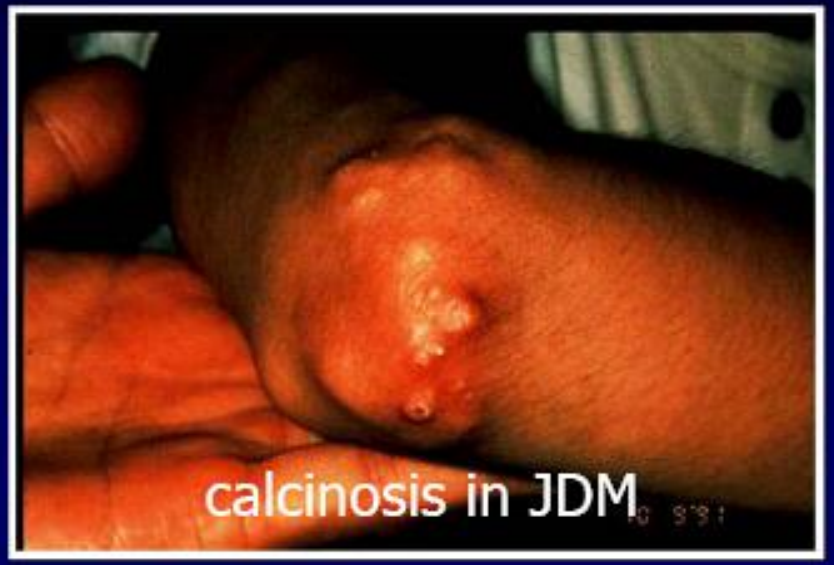
Erythematous rashes over the shoulder, proximal arms and upper back

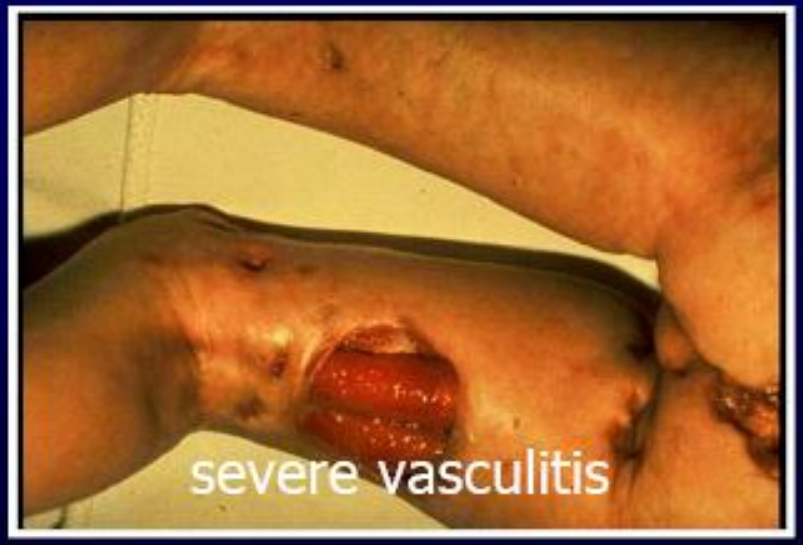


Holster-sign rash: erythematous rash over lateral aspect of proximal thighs

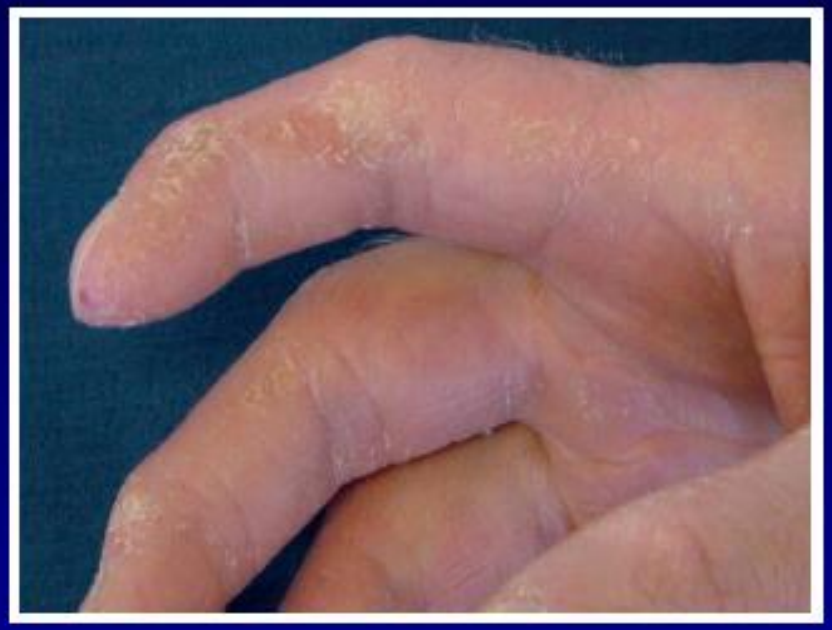


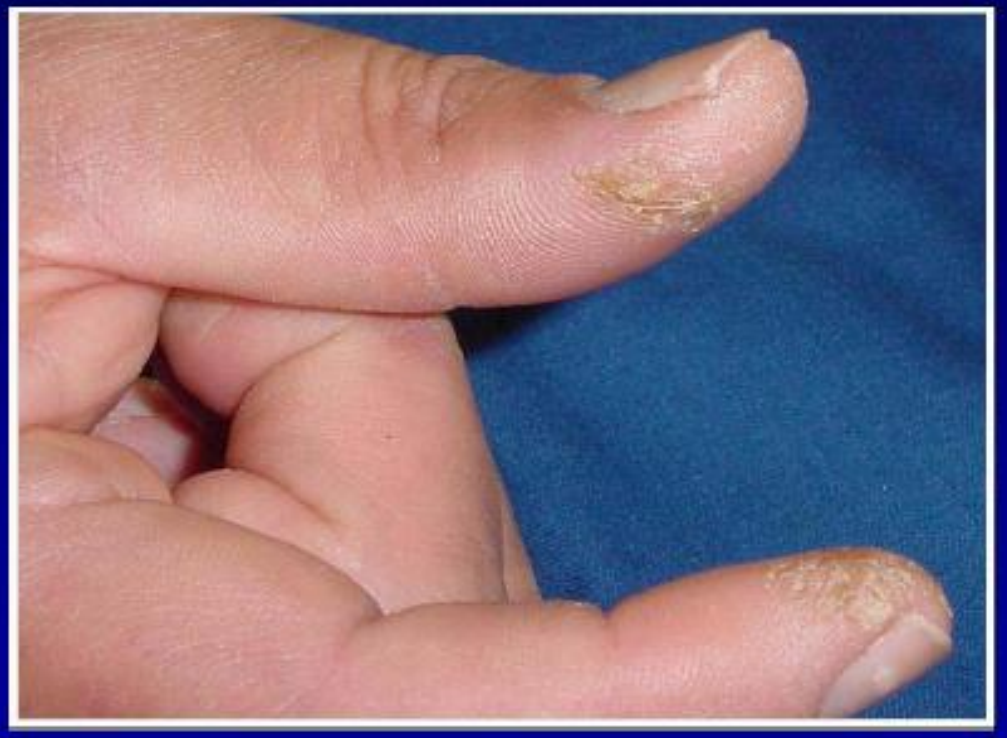
Other Rashes of DM





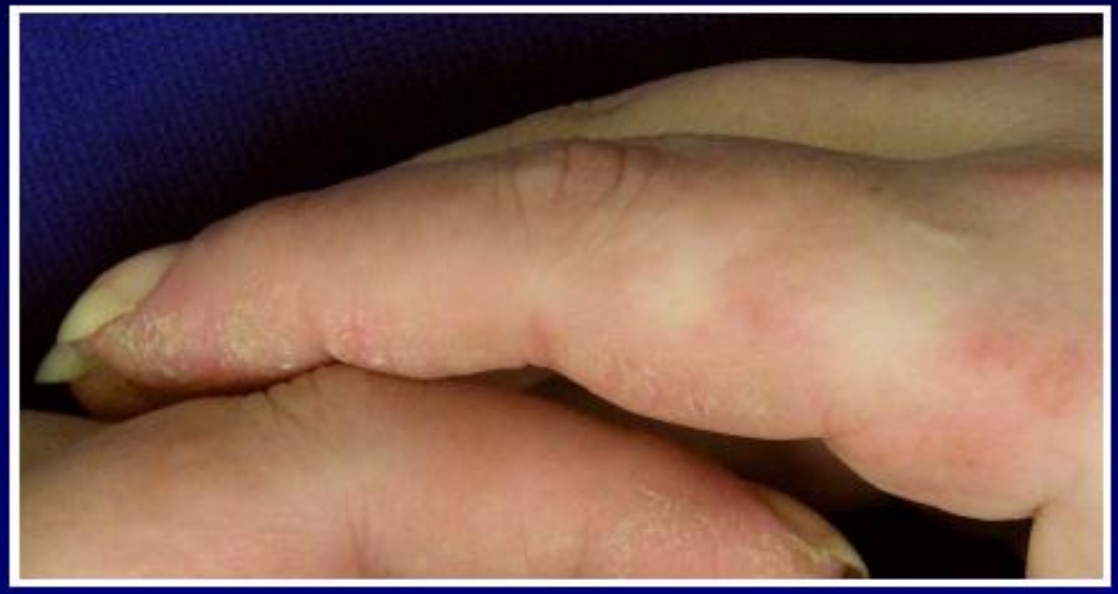
Mechanic's Hands



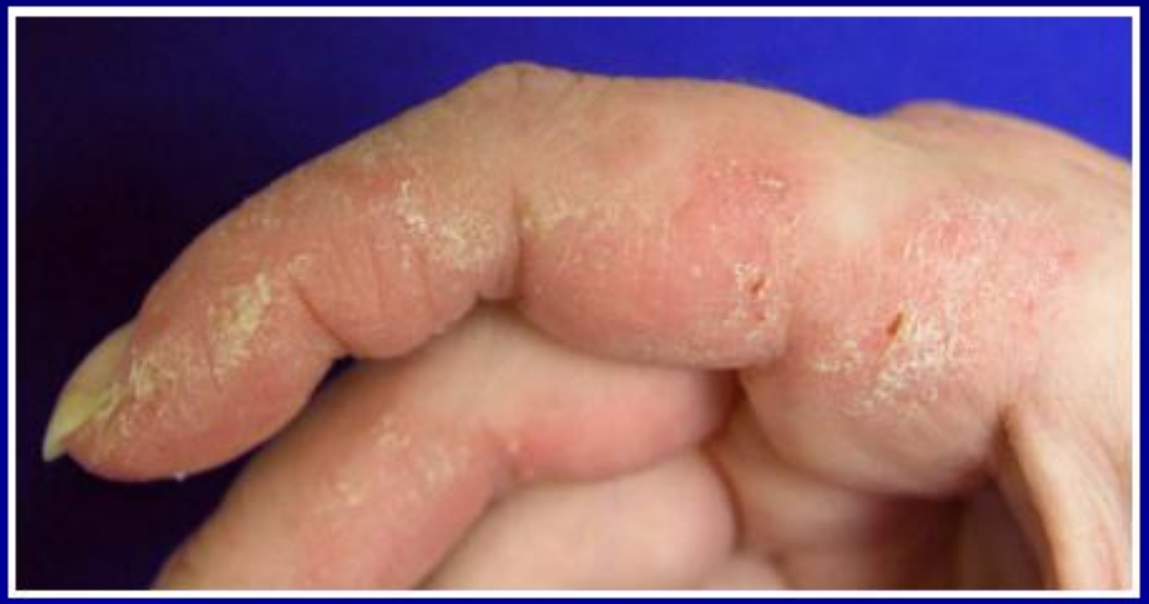


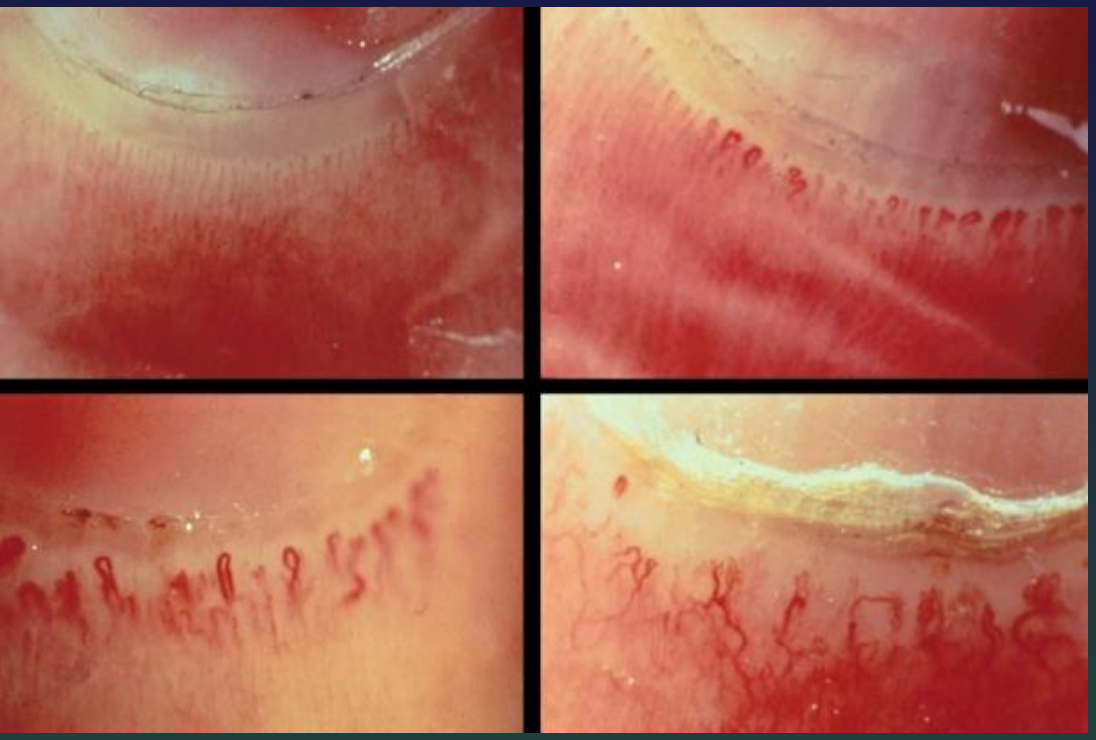
Cracking and fissuring of the skin of the finger pads

Mechanics Hands



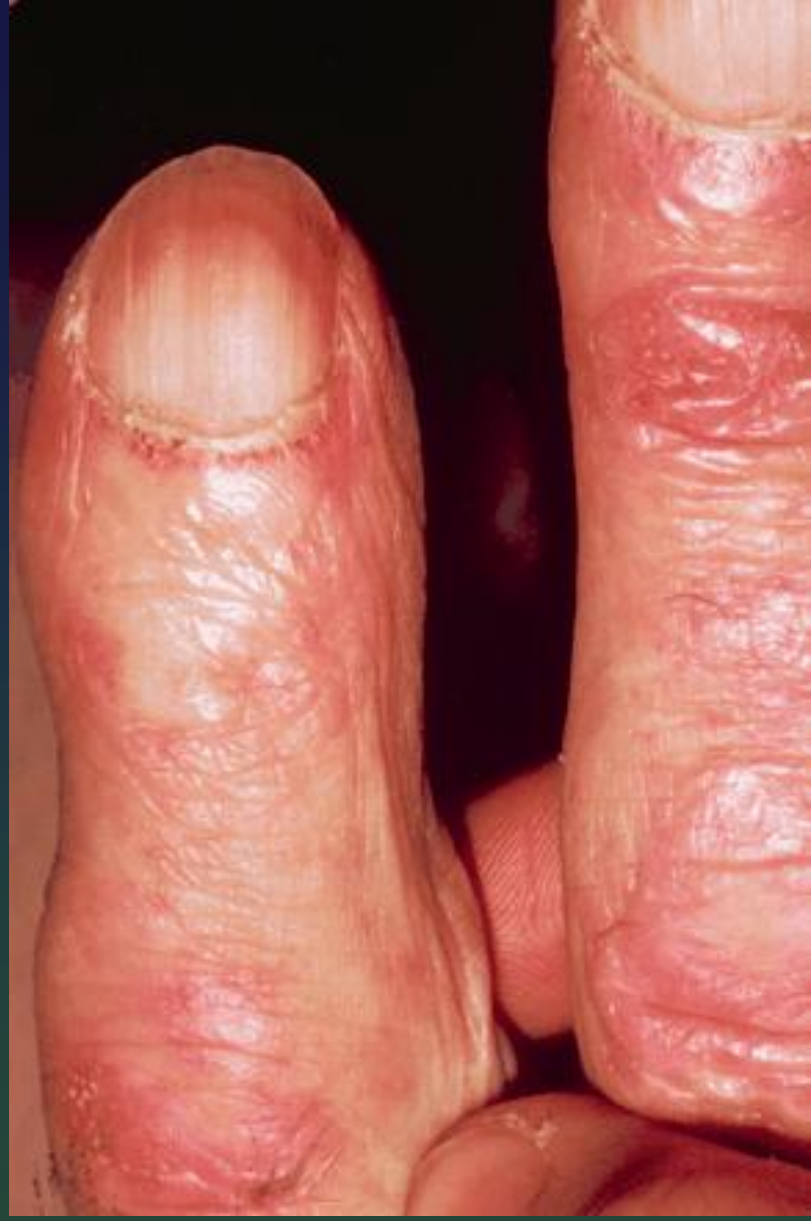
13 days later





Nail fold abnormalities:

- Periungual erythema,
- Cuticular overgrowth,
- Dilated capillary loops .



Nail fold erythema, telangiectasia and ragged cuticles in a patient with dermatomyositis and breast cancer .

GROUP III:
PM or DM with Neoplasia

- Occurs in 10-20% of adults with of PM/DM at time of diagnosis or during follow up (usually 3 – 5 yrs).
- 3–6 times increased risk for malignancy in DM and a 1.4–2 times increased risk for PM.
- Incidence is higher in patients with DM > 60 yrs.
- Most common malignancies are: lung, ovary, breast, GIT, pancreas and Hodgkin's lymphoma.

GROUP III:
PM or DM with Neoplasia

- Association of **Anti-155/140**, directed against the transcription intermediary factor 1 (TIF-1) family proteins with adult cancer-associated DM.
- Anti-Jo-1 and anti-Mi-2 have a negative association with malignancy
- Ulcerative skin lesions in an adult DM patient are highly associated with an underlying malignancy

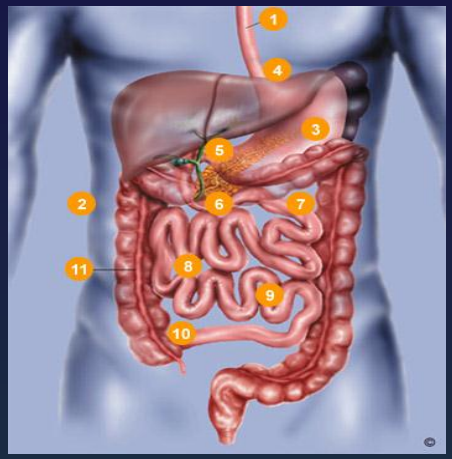
GROUP IV:

Childhood PM or DM associated with Vasculitis

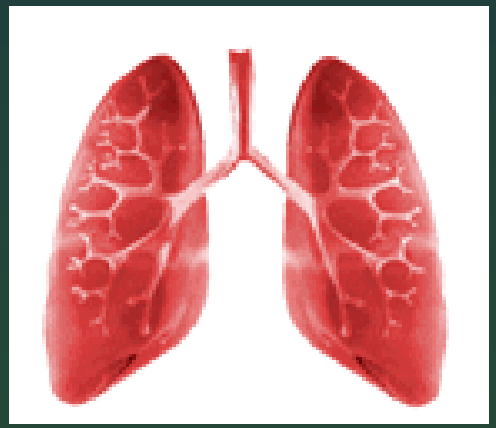
- Comprises ~ 8-20% of all cases of myositis.
- Vasculitis can involve skin, kidneys, GIT, muscle and brain.
- SC calcification is frequently present in childhood DM.

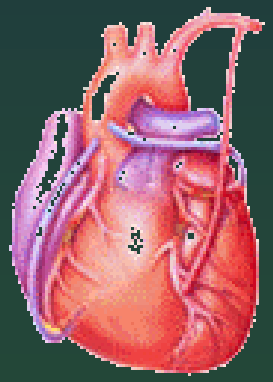
GROUP V:
PM OR DM with an associated CTD.

- Overlap group of myositis and one of the CTD's like SLE, RA, systemic sclerosis and MCTD
- PAN and rheumatic fever rarer association.
- CTD's producing arthritis may cause muscle weakness with fiber atrophy, but without myositis



Systemic complications of PM/DM

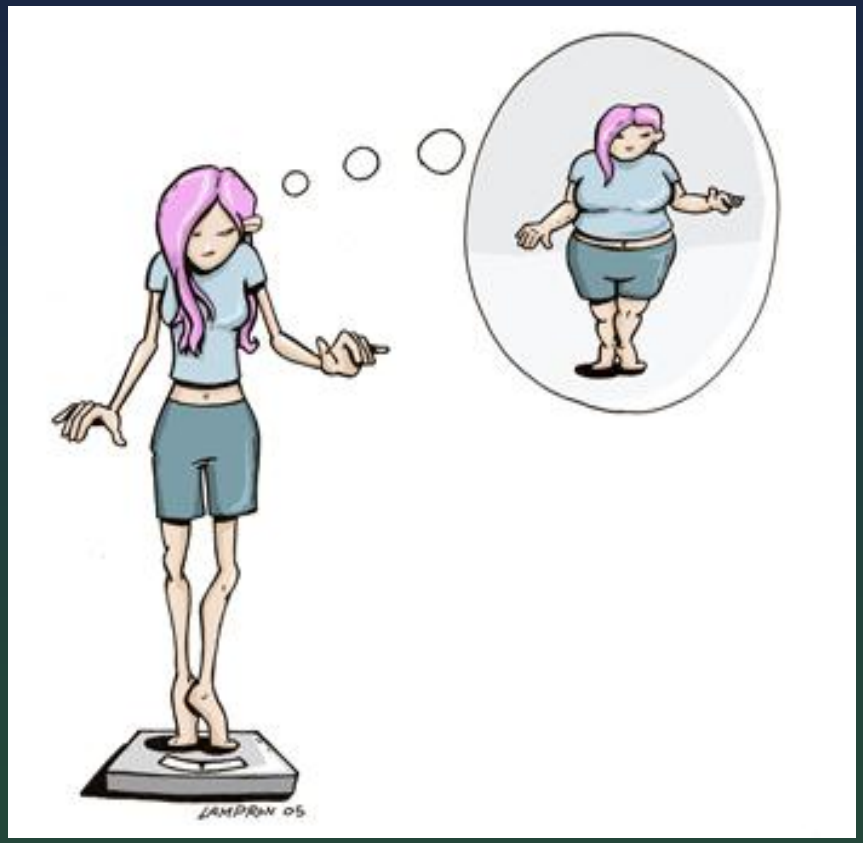




Constitutional symptoms

Fatigue, malaise

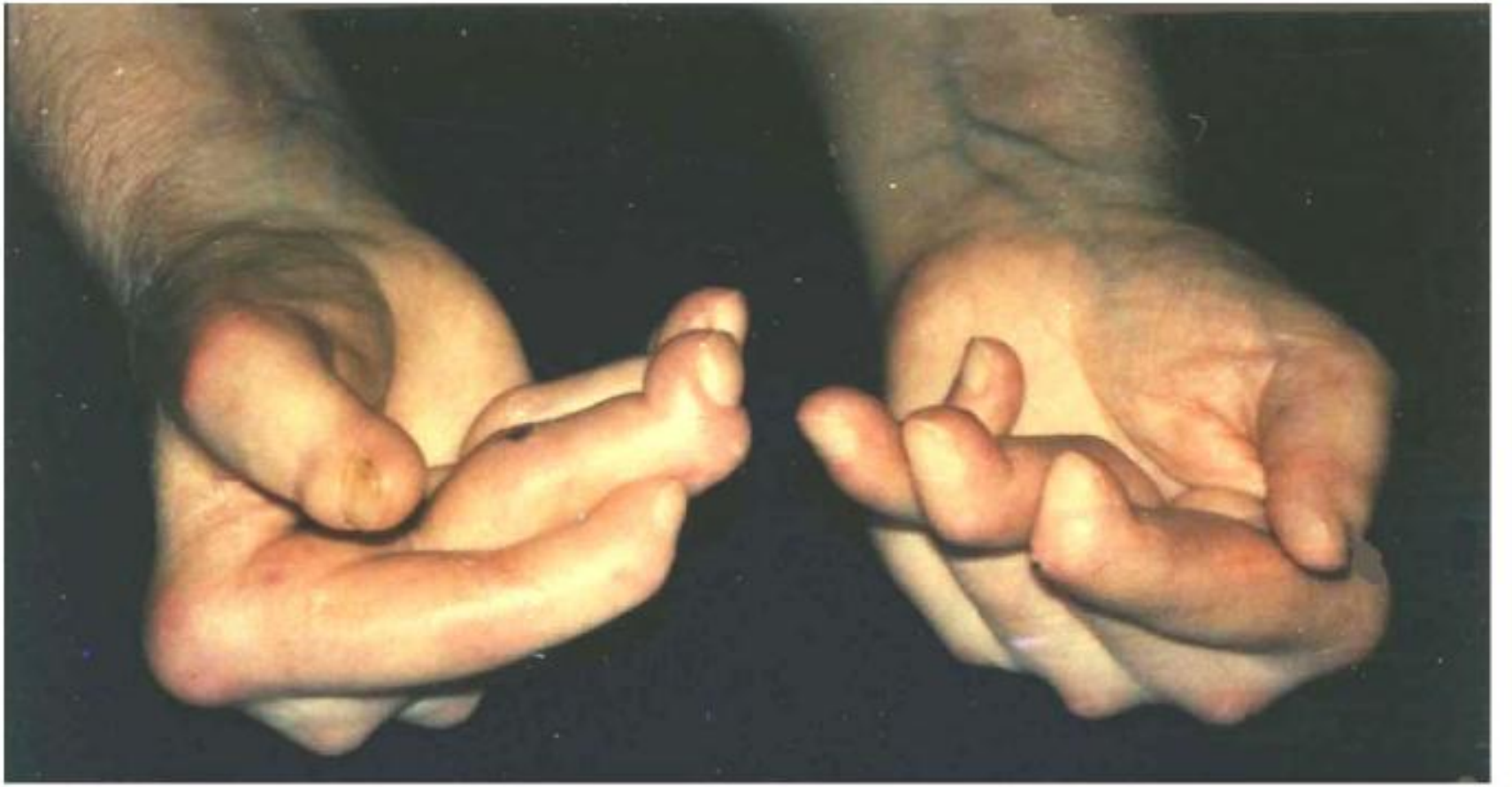
Low grade fever



Weight loss

ARTHRITIS

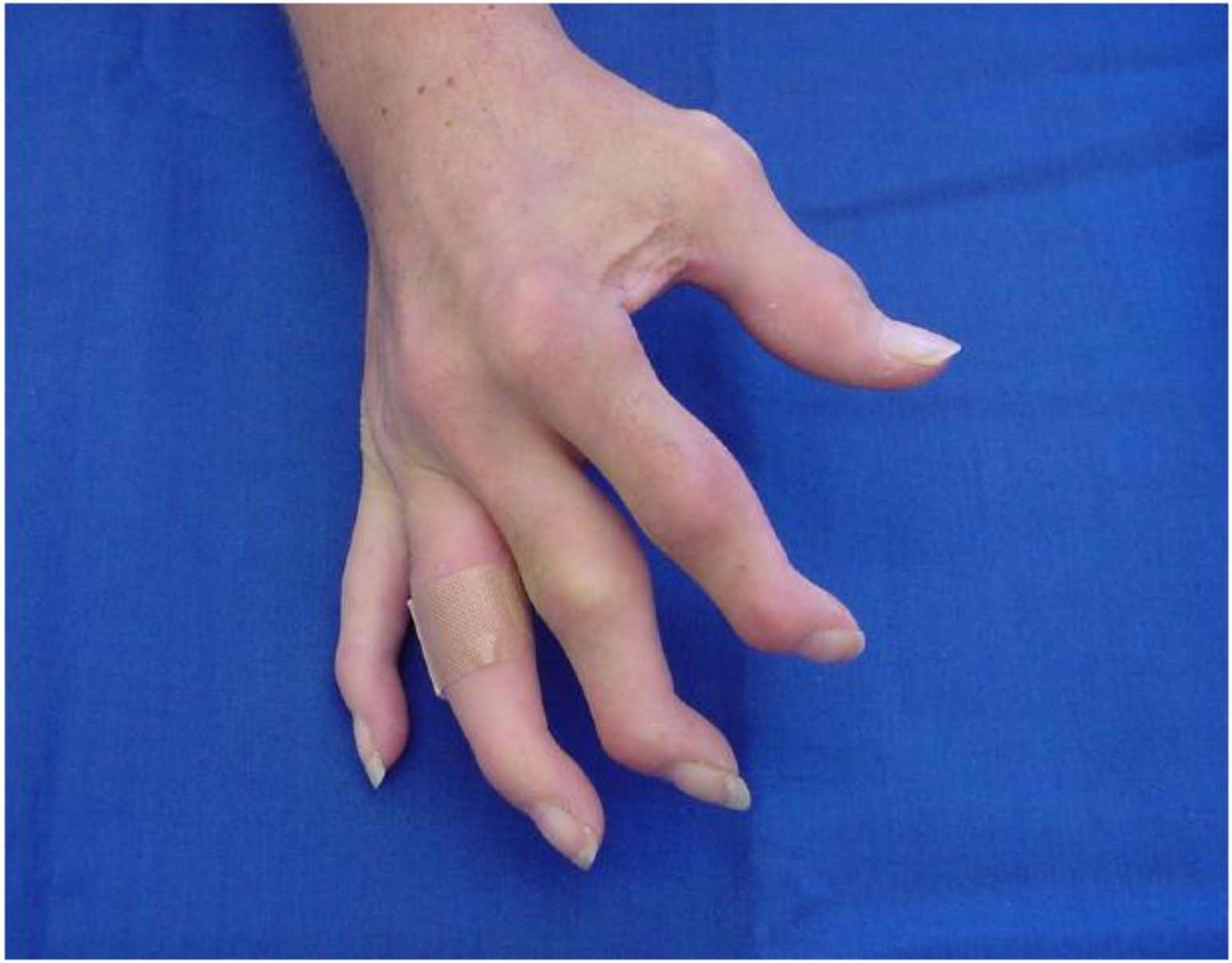
Deforming
Non-erosive



This patient looks like they have rheumatoid arthritis

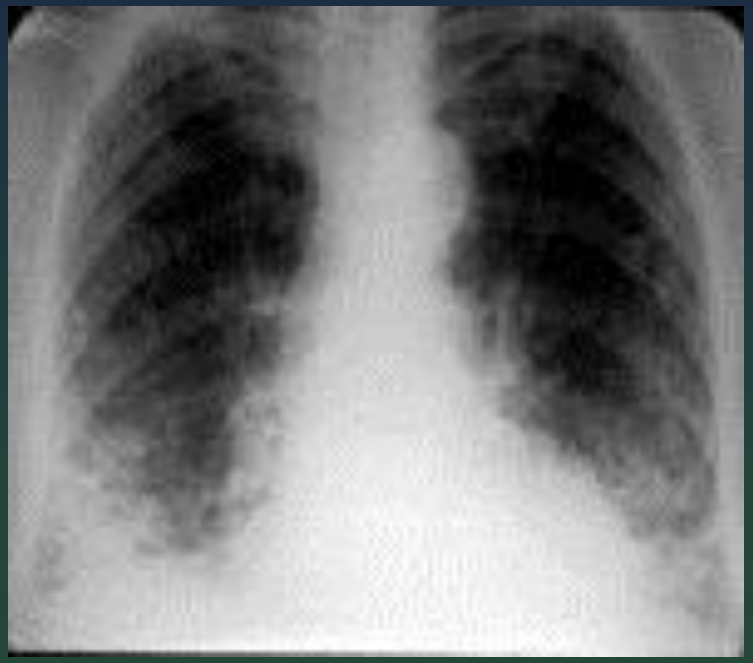
... but they also have myositis

ARTHRITIS



Lung

Lung involvement causes shortness of breath



Airways disease

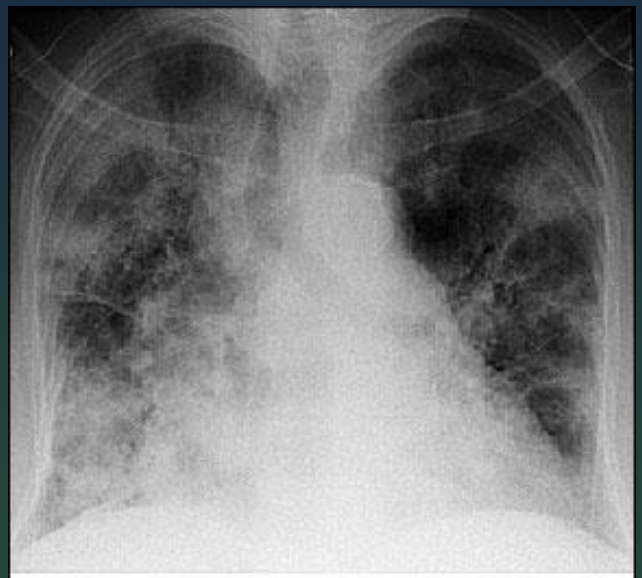
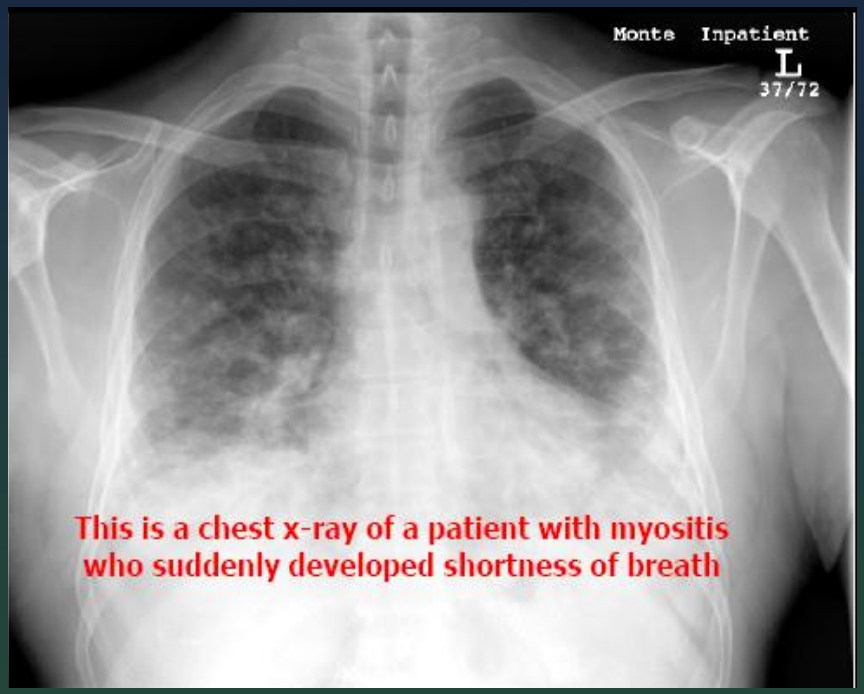


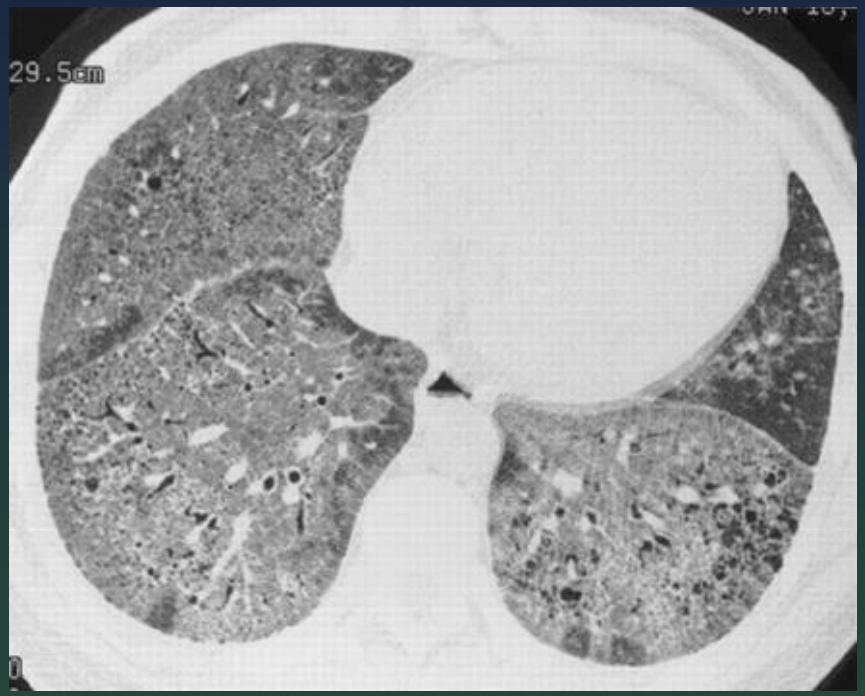
Figure 1—The admission chest radiograph is showing extensive bilateral alveolar and interstitial infiltrates.

Fibrosing alveolitis

Bronchiolitis obliterans organizing pneumonia BOOP*

Lung

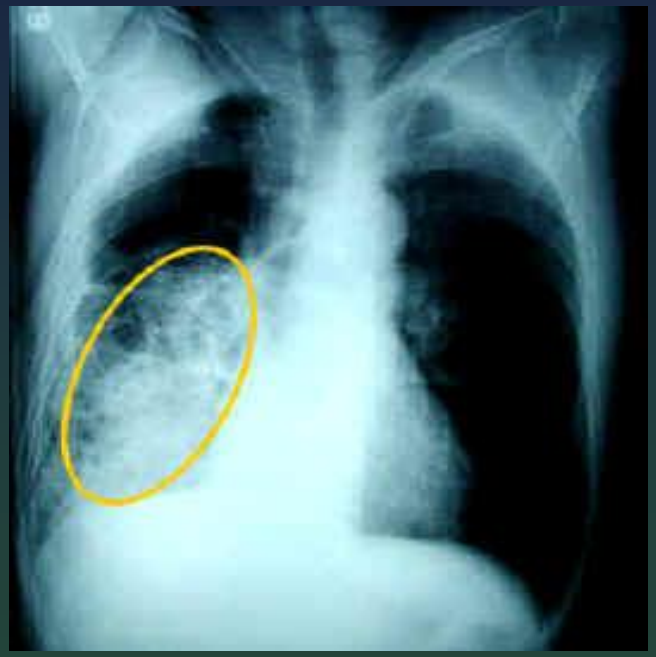




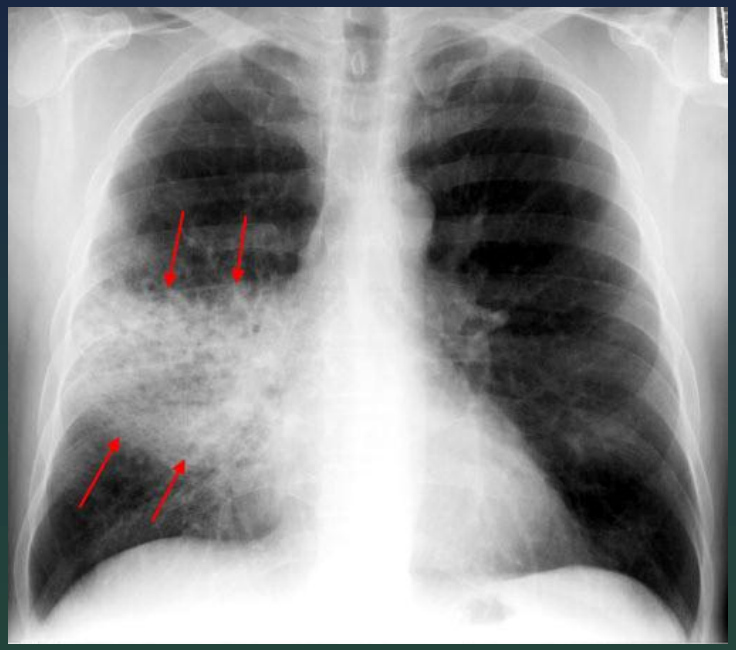
Parenchymal disease

- **Interstitial fibrosis* (10%)**
- Diffuse alveolar damage.

Lung



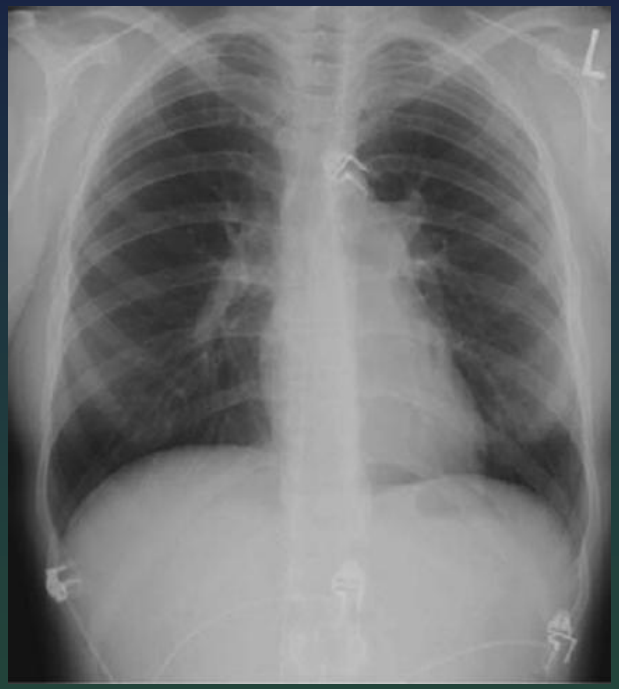
Aspiration pneumonia secondary to dysphagia*



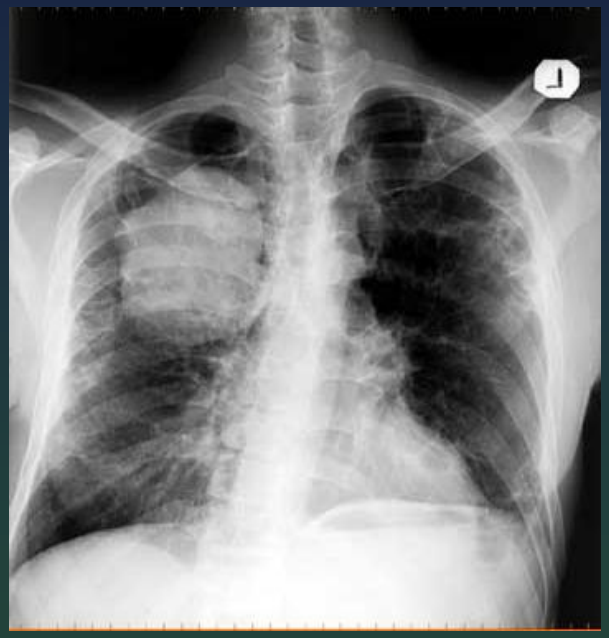
Pneumonia/ opportunistic infections

Secondary features

Lung



Pulmonary HT

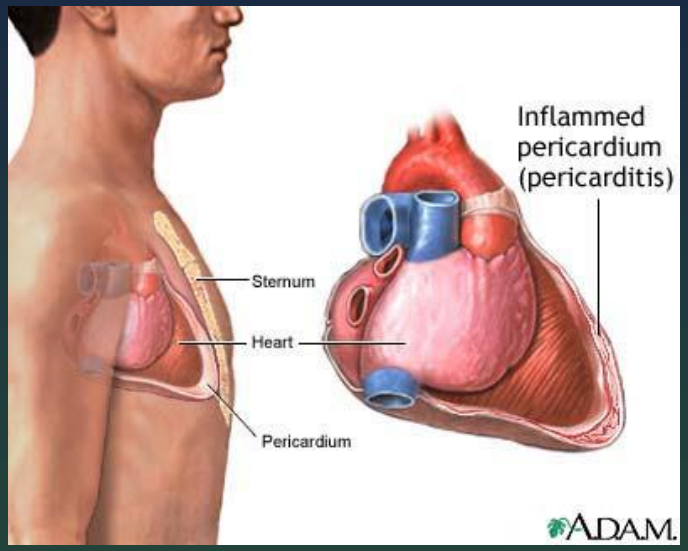


Malignancy, primary or metastatic.

Ventilatory insufficiency 2ry to ms weakness.

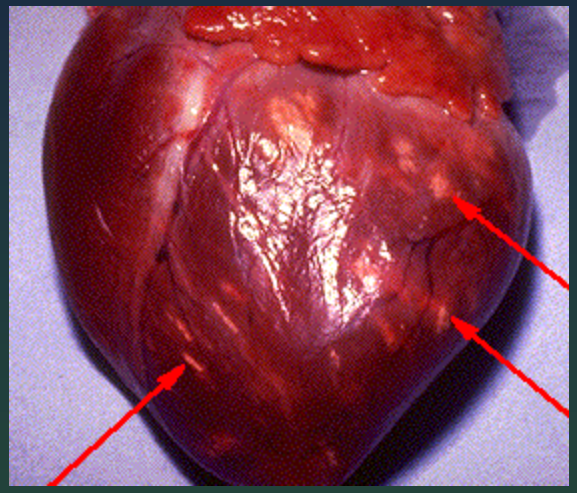
Secondary features

Heart



Pericarditis

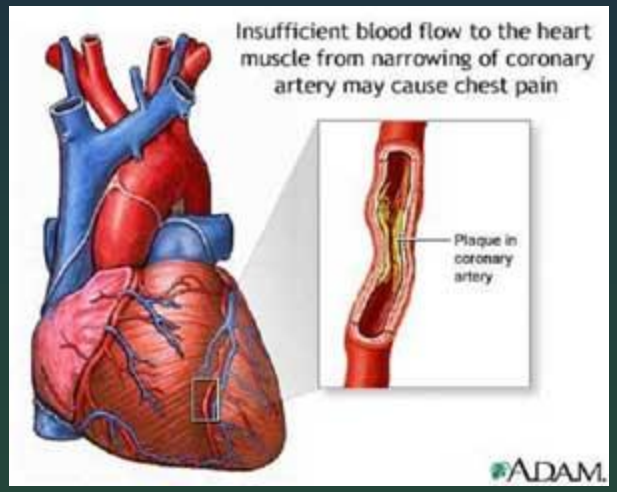
Dilated Cardiomyopathy



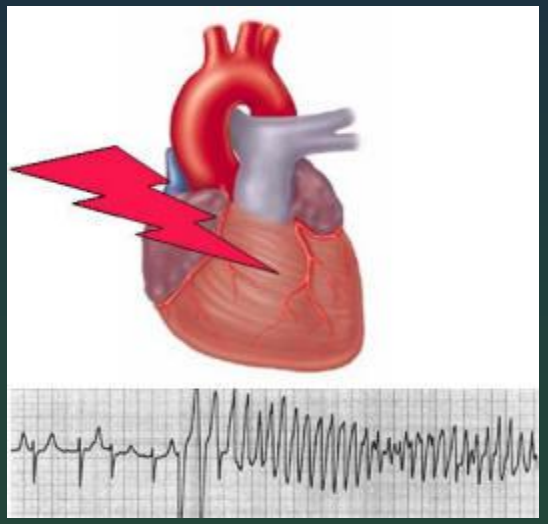
Myocarditis with 2ry fibrosis of the myocardium or the conduction system

Heart

- **Other lesions** due to small-vessel disease :



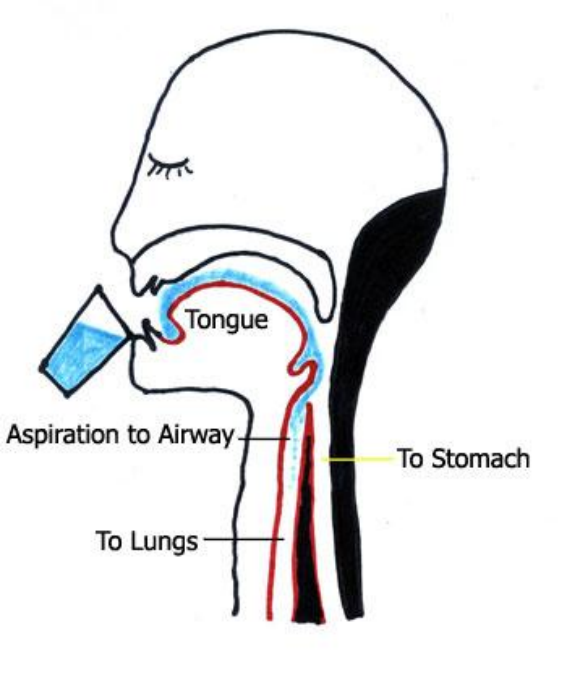
Prinzmetal's angina



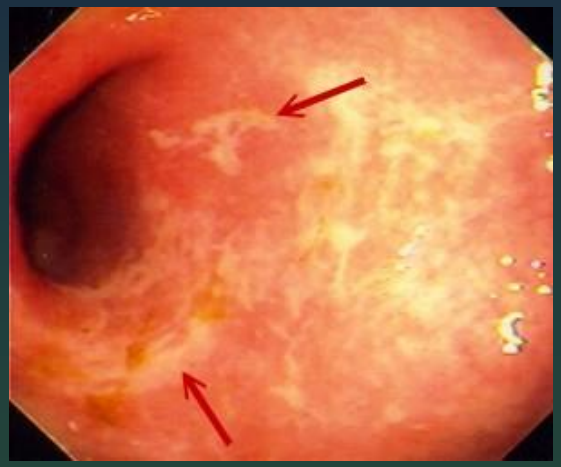
Arrhythmia

Impaired Lt ventricular function compatible with restrictive cardiomyopathy.

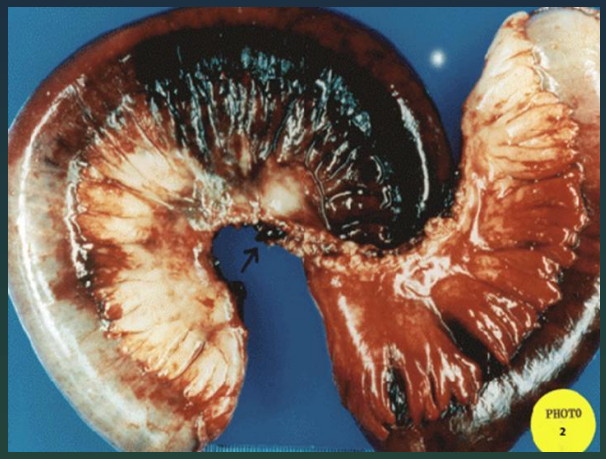
Gastrointestinal Tract



Difficulty swallowing (dysphagia)

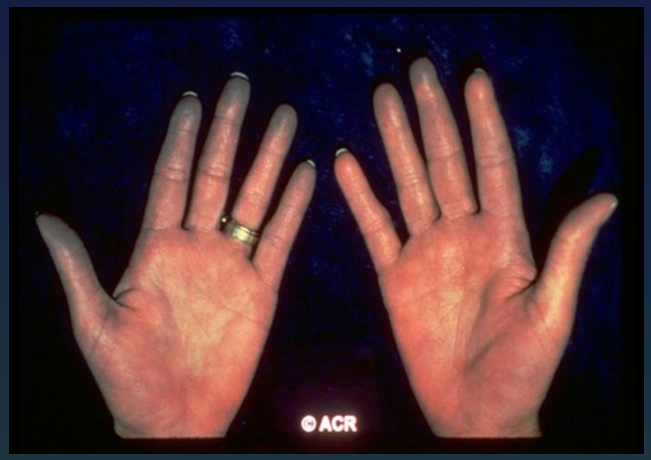


Ulcerations

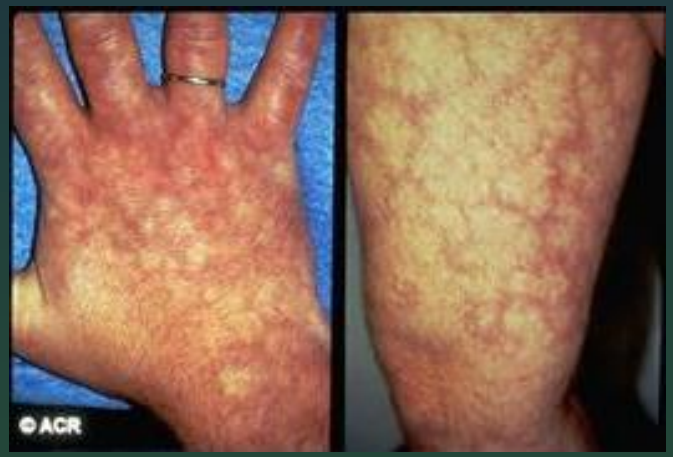


- **Infarction**
- **Perforation**

Vasculitis causing:

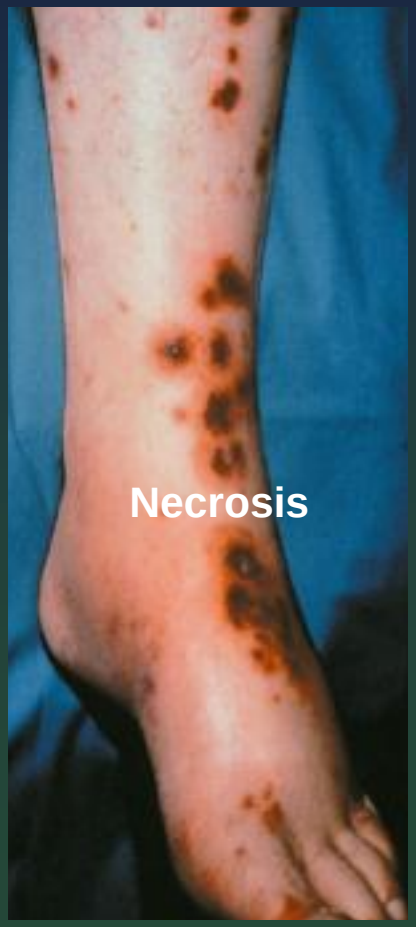


Raynaud's phenom (20-40%)



Livedo reticularis

Skin ulcerations (juvenile DM)



Necrosis

DIAGNOSIS

- **Blood Tests**
  - ↑CK, often >10 times normal
  - Typical ↑ CK-MB > 2%
  - ↑ Troponin I in PM/DM patients with myocardial involvement.
  - ↑ AST, ALT, LDH and aldolase
  - ↑ESR in 50%

DIAGNOSIS

- Myositis associated autoantibodies:
  - ANA: 50-80%. If very high, suggest overlapping CTD
  - Anti-RNP: MCTD & overlap syndromes
  - Anti-PM-Scl: PM- scleroderma overlap
  - Anti-KUl: PM- scleroderma overlap
- Myositis-specific autoantibodies:➔➔>>

DIAGNOSIS

Myositis associated autoantibodies:

	Anti-Synthetase (e.g Anti-Jo)	Anti-SRP	Anti-MI-2
Onset	Acute, spring	Very acute, winter	Acute.
Clinical	**PM>DM** Myositis, ILD, small J. arthritis, Raynaud's, Mechanics hand	**Severe PM necrosis** Cardiac involvement	**Classic DM** V-, Shawl rashes Periungual erythema Cuticular overgrowth
Steroid response	Moderate	Poor. 5-yr survival 30%	Good 5-yr survival 30%

Table 20-1. Myositis-specific Autoantibodies

AUTOANTIBODY	ANTIGEN	PREVALENCE PM/DM	CLINICAL ASSOCIATION	HLA DISSOCIATION
Antisynthetase*	Aminoacyl-tRNA synthetase	20% to 50%	Antisynthetase syndrome	DRw52, DR3
Anti-SRP	Signal recognition particle	5%	Severe, resistant PM	DRw52, DR5
Anti-Mi-2	Helicase components of histone deacetylase complexes	5% to 30%	Classic DM	DRw53, DR7

*Frequency in idiopathic inflammatory myositis: anti Jo-1 (histidyl) (15% to 20%), PL-7 (threonyl) (5% to 10%), PL-12 (alanyl) (<5%), EJ (glycyl) (5% to 10%), OJ (isoleucyl) (<5%), KS (asparaginyl) (<5%), Zo (phenylalanyl) (<1%), Ha-YRS (tyrosyl) (<1%), Mas (serine) (<1%).

DIAGNOSIS

Myositis associated autoantibodies:

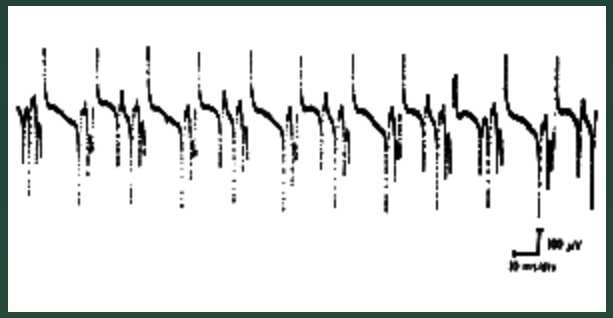
	Anti-155/140	Anti-MDA-5 (anti-CADM-140):	Others
Clinical	**Juvenile DM** Adult cancer-associated DM Heliotrope rash Gottron papules Low titer ANA (speckled and homogeneous)	**DM** skin ulceration, palmar papules, rapidly progressive ILD 80% amyotrophic DM (20%)	- anti-SSAE (5% DM patients); - anti-PMS-1 (7% PM/DM patients) - anti-MJ (NXP-2) (25% of juvenile DM especially with calcinosis).

DIAGNOSIS

- **ECG abnormalities** in 10%
- **EMG triad** (in 40% of cases):
  1) Positive sharp waves and insertional irritability
  2) Small (low amplitude) polyphasic action potentials,
  3) Bizarre high frequency repetitive discharges

May distinguish myopathic from NMJ and neuropathic disorders.

	Lesion / EMG Steps	Normal	Neurogenic Lesion		Myogenic Lesion	
			Lower Motor	Upper Motor	Myopathy	Polymyositis
1	Insertional Activity	Normal	Increased	Normal	Normal	Increased
2	Spontaneous Activity		Fibrillation Positive Wave			Fibrillation Positive Wave
3	Motor Unit Potential	0.5-1.0 mv 5-10 msec.	Large Unit Limited Recruitment	Normal	Small Unit Early Recruitment	Small Unit Early Recruitment
4	Interference Pattern	Full	Reduced Fast Firing Rate	Reduced Slow Firing Rate	Full Low Amplitude	Full Low Amplitude



Bizarre high frequency repetitive discharges

DIAGNOSIS

- **CXR, mammograms, abdominal/pelvic CT** & **other screening tests** might be considered for possible malignancy.
- **MRI:**
  - rule out other diseases that might mimic myositis,
  - direct muscle biopsy in difficult cases.

DIAGNOSIS

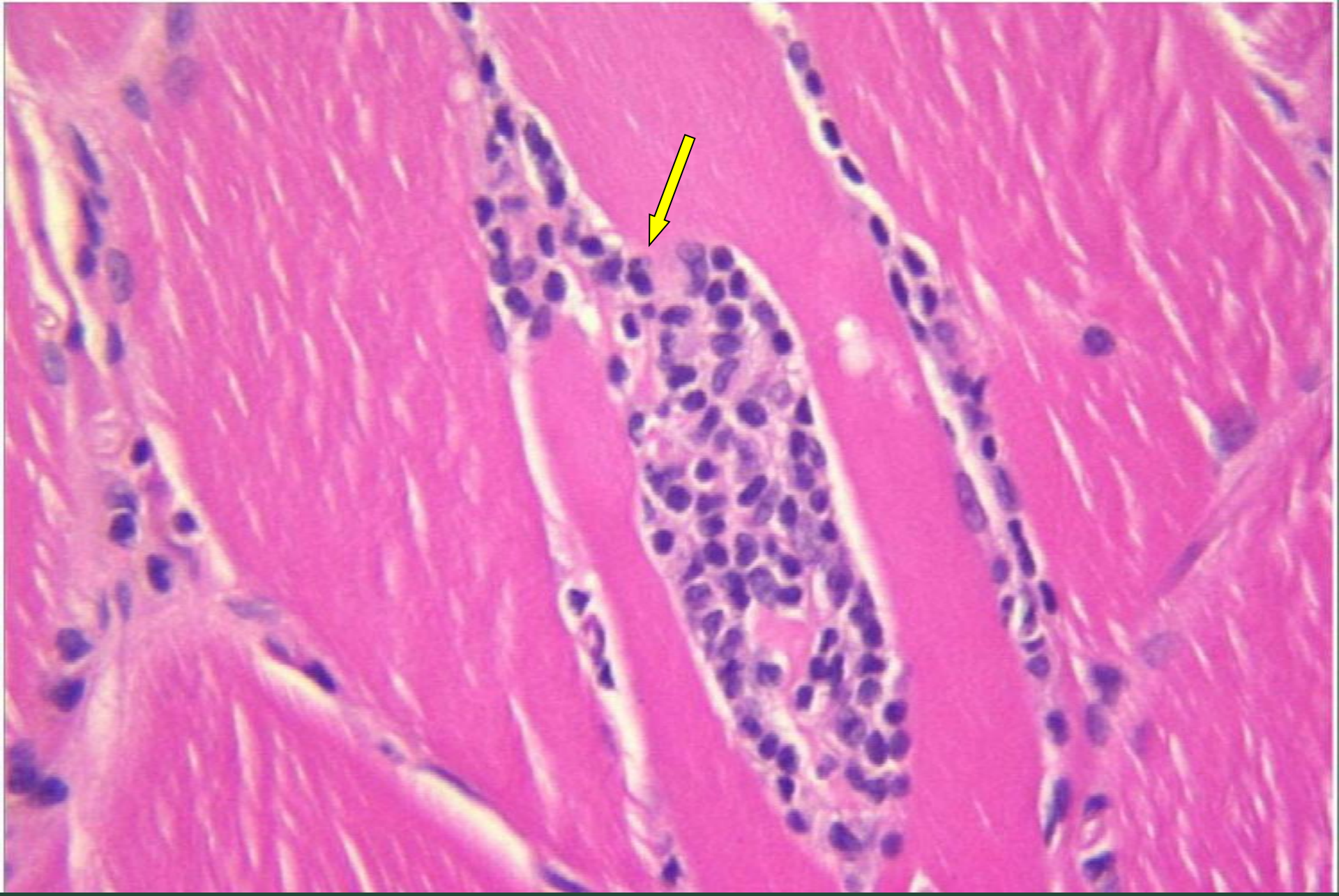
Muscle Biopsy

- In PM, perifascicular infiltrates of inflammatory cells CD8+ T cells leading to **perifasicular atrophy of muscle fiber**. No vasculopathy.
- In DM perivascular & perifascicular infiltrates of CD4> CD8 T cells and B-cells w/ microinfarct of ms. fibers
  - Upregulation of MHC Class I antigens on muscle fibers in the perifasicular areas is common.

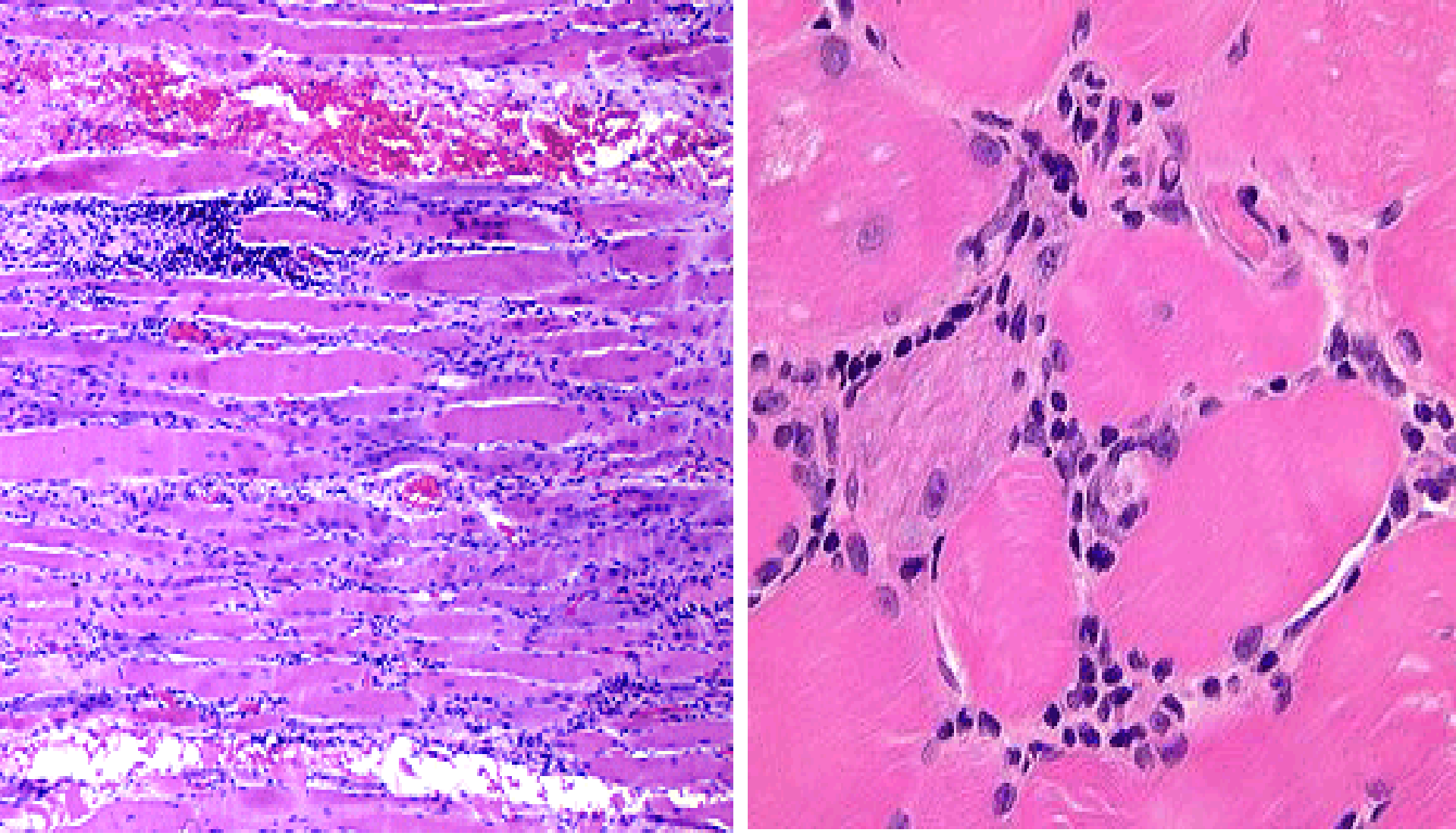
DIAGNOSIS

Muscle Biopsy

- Necrotizing autoimmune myopathy (NAM):
  - Invasion of macrophages but a lack of lymphocytic infiltrates and lack of widespread MHC Class I upregulation on muscle fibers.
  - Marked muscle necrosis with regeneration.
  - Associated with anti-SRP syndrome, statin therapy, malignancy, HIV-associated myositis, some pts w/ the antisynthetase syndrome.
- Unspecified myositis: second most common pattern.
  - Inflammatory infiltrate without specific localization or upregulation of MHC Class I expression.
  - Commonly seen in overlap myositis, especially anti-Ku & anti-PM-Scl.



Lymphocytes “attacking” normal muscle tissue
Result: muscle weakness



Interstitial inflammation in polymyositis Low (left panel) and high (right panel) views of muscle biopsy in polymyositis. There is an intense interstitial mononuclear infiltrate with some myocyte degeneration. Courtesy of Cynthia Magro, MD and William W Pendlebury, MD.

Diagnostic Criteria of PM/DM

MAJOR CRITERIA

1. Symmetrical proximal ms. weakness.
2. Elevated muscle enzymes.
3. EMG triad.
4. Muscle biopsy
5. Dermatological component:
   - heliotrope with periorbital edema, gottrons sign,
   - involvement of knees, elbows, medial malleoli, face and upper torso

Diagnostic Criteria of PM/DM

- **Definite :**
  Polymyositis: 4 criteria (without rash).
  Dermatomyositis: 3 criteria plus the rash.
- **Probable :**
  Polymyositis: 3 criteria without rash.
  Dermatomyositis: 2 criteria plus the rash.
- **Possible :**
  Polymyositis: 2 criteria without the rash.
  Dermatomyositis: 1 criteria plus the rash.

Treatment of PM/DM

- **Prednisone** 1-2mg/kg/day, tapered after strength improves and CK declines, often after 1-3 mo. Consider IBM (poor response)
- **Immunosuppressive agents:** introduced if severe disease (dysphagia), relapsing disease, inadequate steroid response or steroid induced side effects.

Treatment of PM/DM

Immunosuppressive agents:

- used with varying success as second-line agents
- **Indications:**

  a. no improvement with steroids within 4 wk

  b. adverse effects from corticosteroids develop.

  c. poor prognostic indicators (dysphagia or dysphonia)

- Methotrexate (up to 25 mg/wk)
- Azathioprine (2 to 3 mg/kg/day)
- Mycophenolate mofetil (1 to 1.5 g BID)
- Hydroxychloroquine: effective in cutaneous DM
- Leflunomide
- Cyclophosphamide

Treatment of PM/DM

- IV **immunoglobulin (IVIG)** (2 g/kg over 5 days [0.4 g/kg/day] initially, followed by monthly 3-day courses).
  Effective in severe, refractory DM e.g. pts with dysphagia
- **Biologics:** role unclear. Infliximab success in few cases
- **Rrituximab**:
  ? effective in some cases w/ myositis-specific antibodies
- **Tacrolimus** (0.1 mg/kg/day; 2 to 5 mg BID) is effective in resistant T cell-mediated PM and lung disease (especially cryptogenic organizing pneumonia).

Treatment of PM/DM

- **Repository corticotropin injection (H.P. Acthar gel):**
- Derived from pituitary glands obtained from pigs.
- It contains ACTH + melanocortins (may have immuno-modulating properties when they bind to one of five melanocortin receptors).
- FDA approved for treatment of resistant DM/PM.
- Each 5-mL vial has a concentration of 80 USP units/mL.
- Dose is 80 USP units SC twice/wk for 3 mo then ↓ dose.
- Combination regimens
- Stem cell transplantation

Treatment of PM/DM

- Rehabilitation:
  - Diet: high protein. Avoid weight gain due to CS use
  - Exercise: initial passive + splint to avoid contracture then active when inflammation subsides, later strengthening
  - Osteoporosis prevention,
  - Speech Rx. (for swallow evaluation)
- If the condition is associated with a tumor, the condition may improve if the tumor is removed.

Prognosis of PM/DM

- **Clinical subgroups:**
- 5-yr survival > 85% in idiopathic PM.

  Poorer prognosis with severe weakness, dysphagia, ILD, respiratory ms weakness, myocardial involvement and associated neoplasm,
- Death may result from severe and prolonged muscle weakness, malnutrition, HF, pneumonia, or respiratory failure.

Prognosis of PM/DM

- **Serological subgroups:**
  - Anti-Mi-2: favorable prognosis w/ 5-yr survival > 90%
  - Anti-synthetase: less favorable, w/ 5-yr survival > 65%
  - Anti-SRP / Anti-MDA-5/anti-155/140 antibodies : worst, w/ 5-yr survival ~ 30%
- **Histogical subgroups:** poor prognosis w/ necrotizing myopathy

Inclusion Body Myositis

- Definition: An acquired muscle disease group over age of 50, characterized by
  - slowly progressive weakness & wasting of both distal and proximal muscles, mostly forarms & legs
  - a pathologic finding of vacuoles & filamentous inclusions
- Types: 1. Sporadic inclusion body myositis
  2. hereditary inclusion body myopathy
- Prevalence: 5-10/million

Inclusion Body Myositis

- Etiology

❑ Unknown

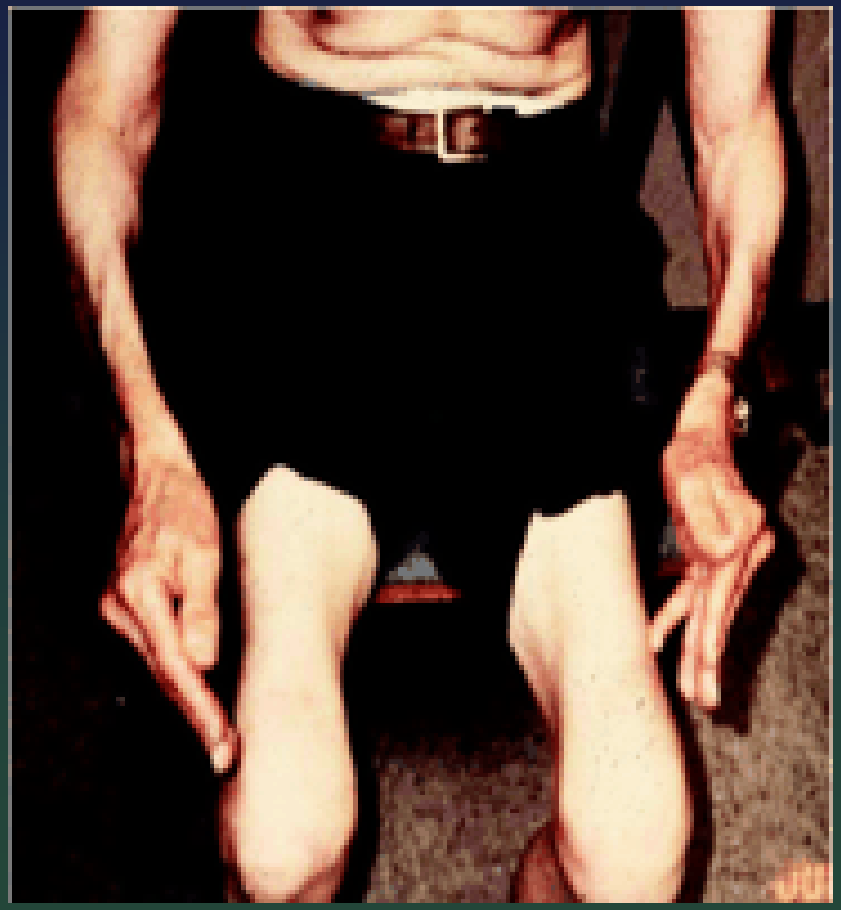
❑ Interaction of genetic and environmental factors that trigger inflammatory-immune reaction

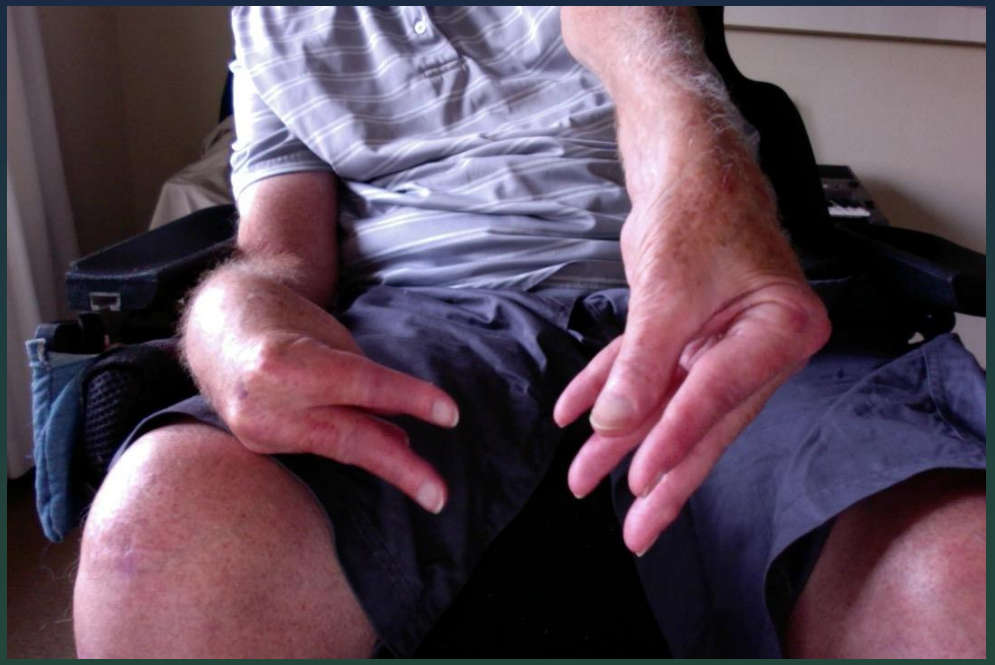
❑ Evidence for autoimmune/immunologic cause:

- association with other autoimmune disorders
- blood tests findings: “autoantibodies”
- muscle biopsy “resembles” polymyositis

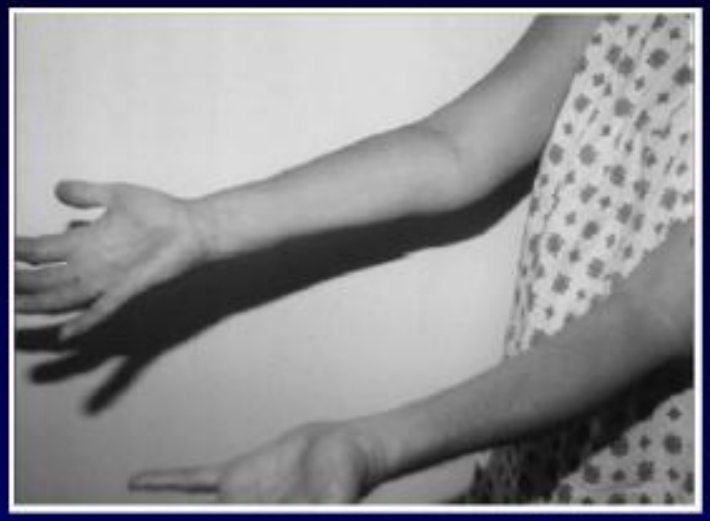
Inclusion Body Myositis

- Pathogenesis
- Inflammatory: 1ry T-cell mediated autoimmunity
- Degenerative involving abnormal protein processing →2ry inflammatory response
- Separate and independent immune and degenerative process caused by external trigger
- C/P
- Falling down Difficulty to perform ADL
- Weakness & wasting of finger flexors (making fist), quadriceps and anterior tibial group (foot drop)
- Dysphagia (40-85%) → aspiration pneumonia

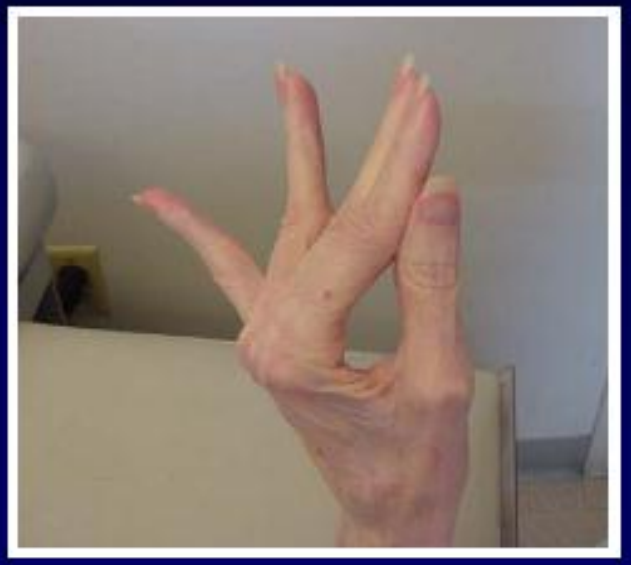




Inclusion Body Myositis

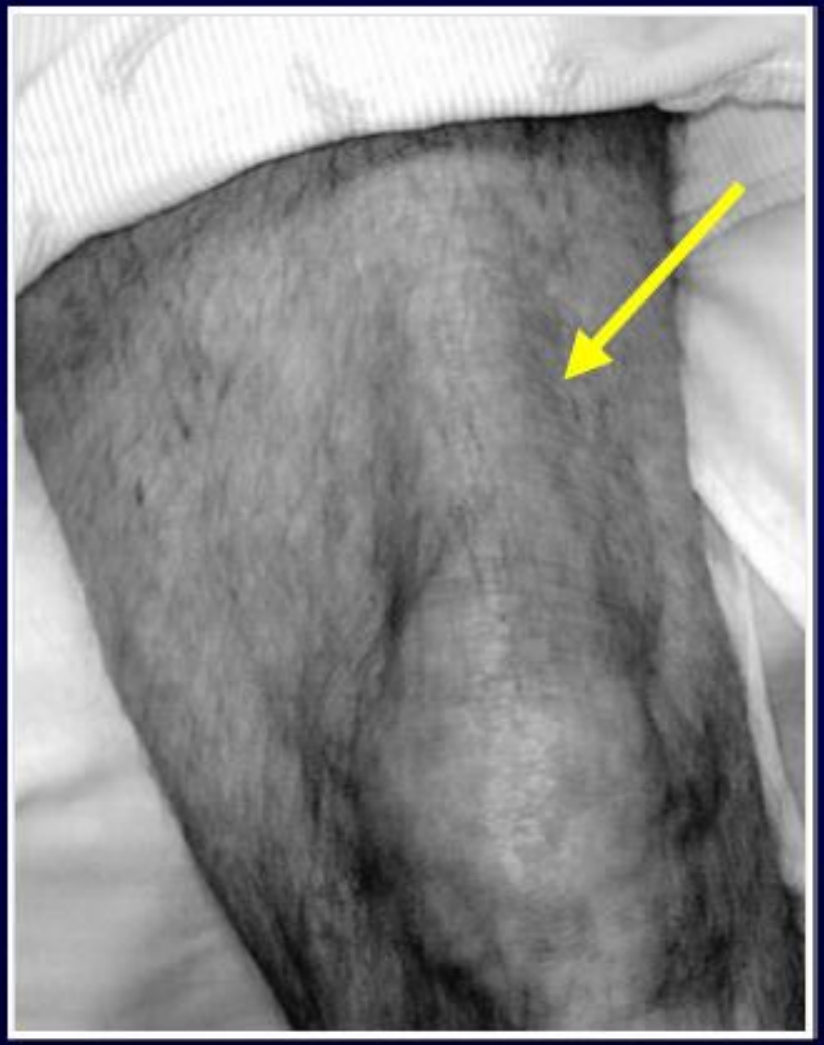


"scooped out" forearm



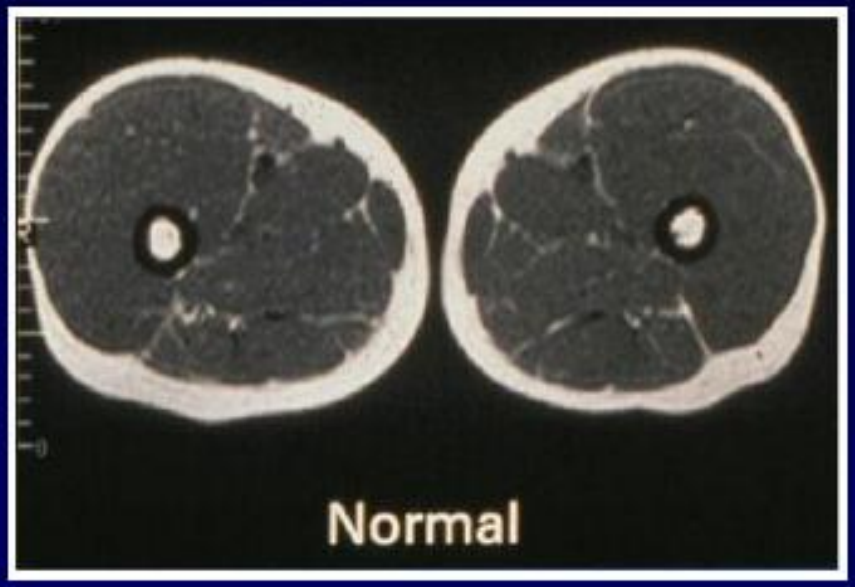
"teardrop sign"

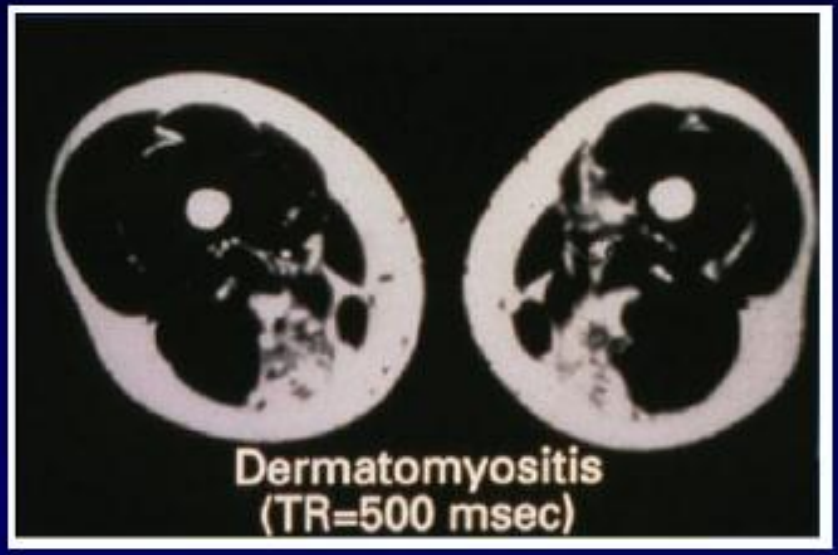
IBM: Quadriceps Atrophy

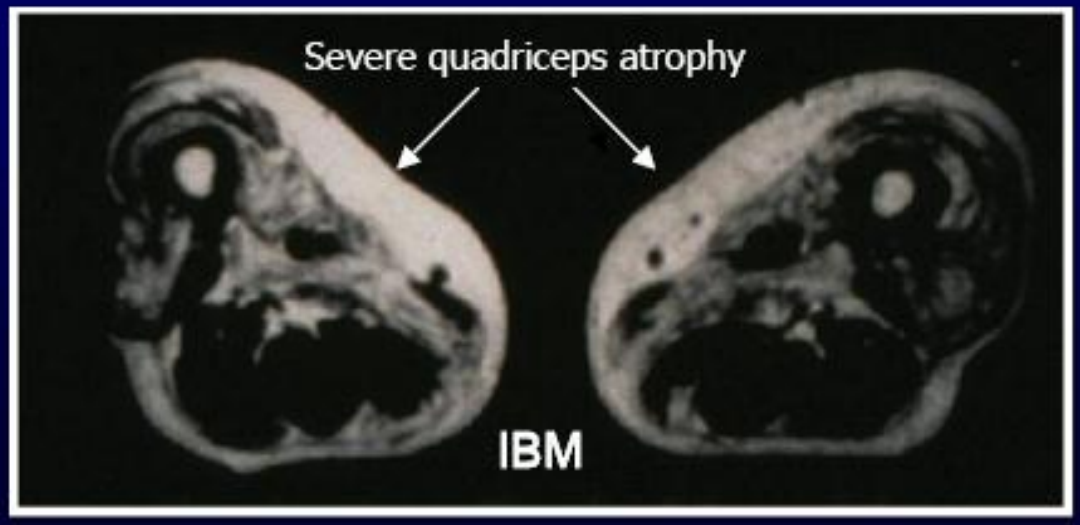


Felice, Medicine, 2001

MRI of Muscle

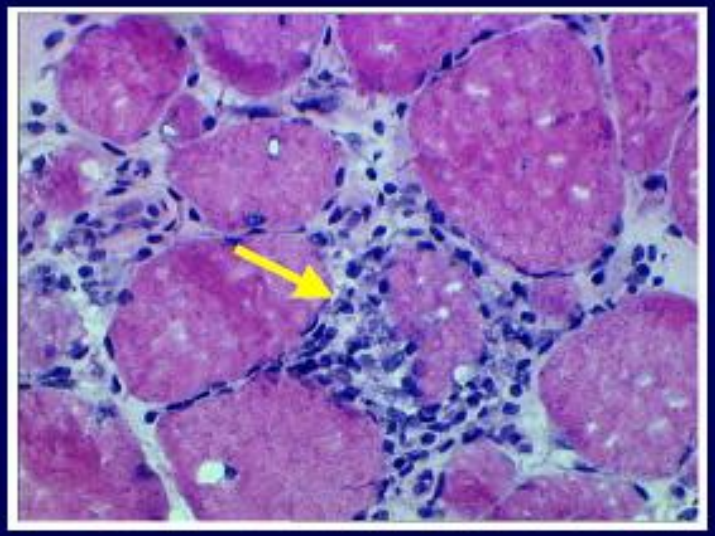


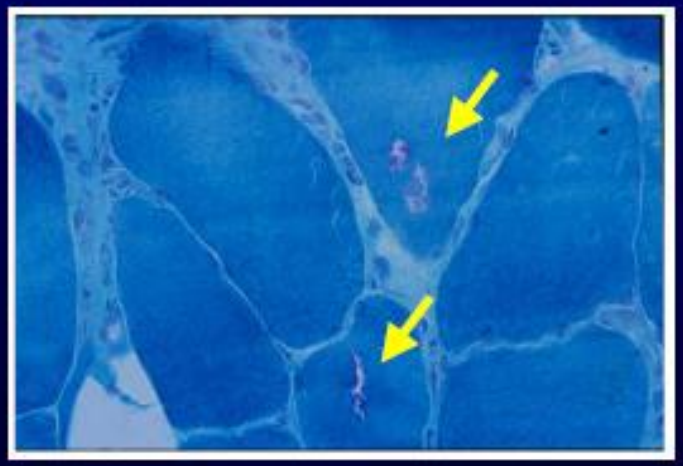


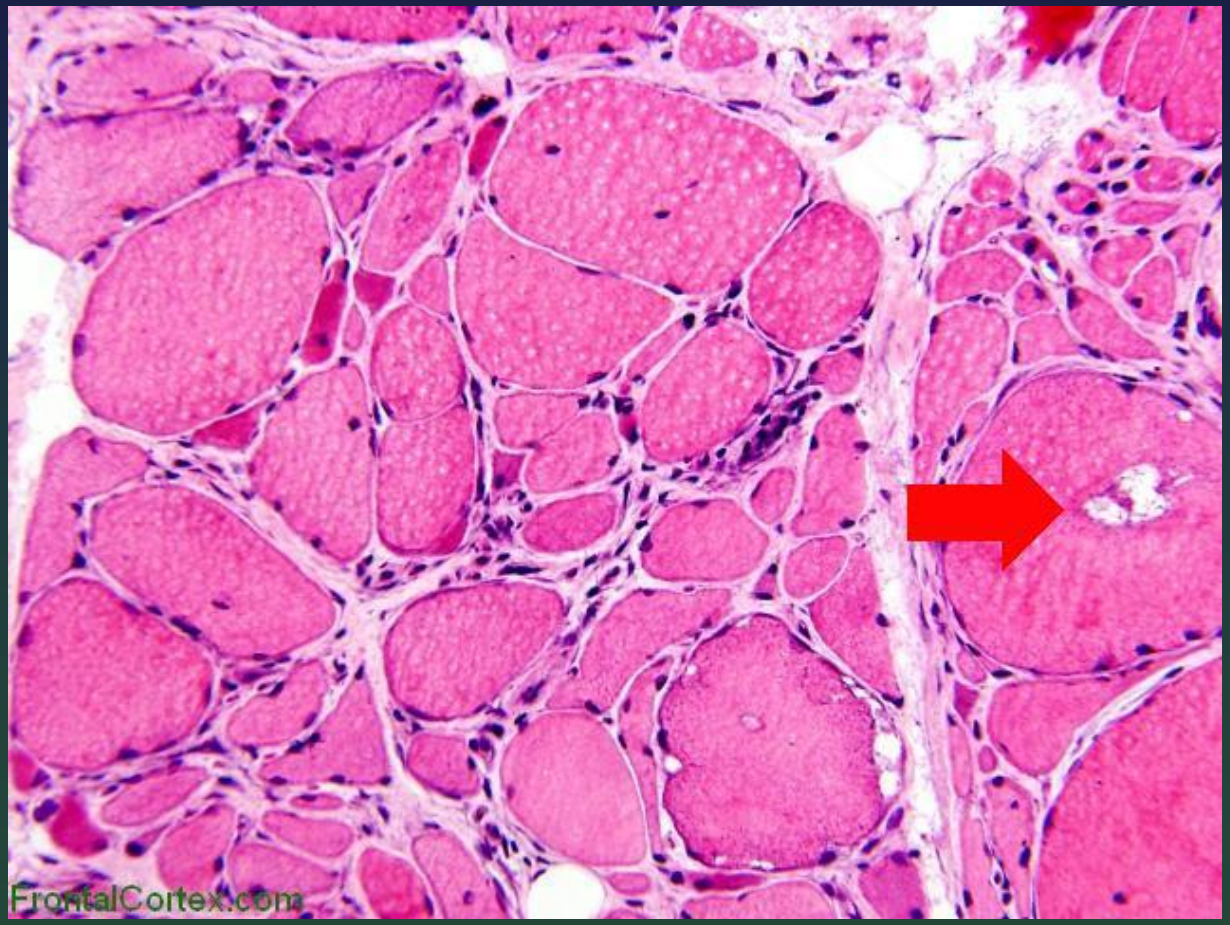


Inclusion Body Myositis: Muscle Pathology

- Distinctive histology:
  - inflammation
  - rimmed vacuoles/red "inclusions"



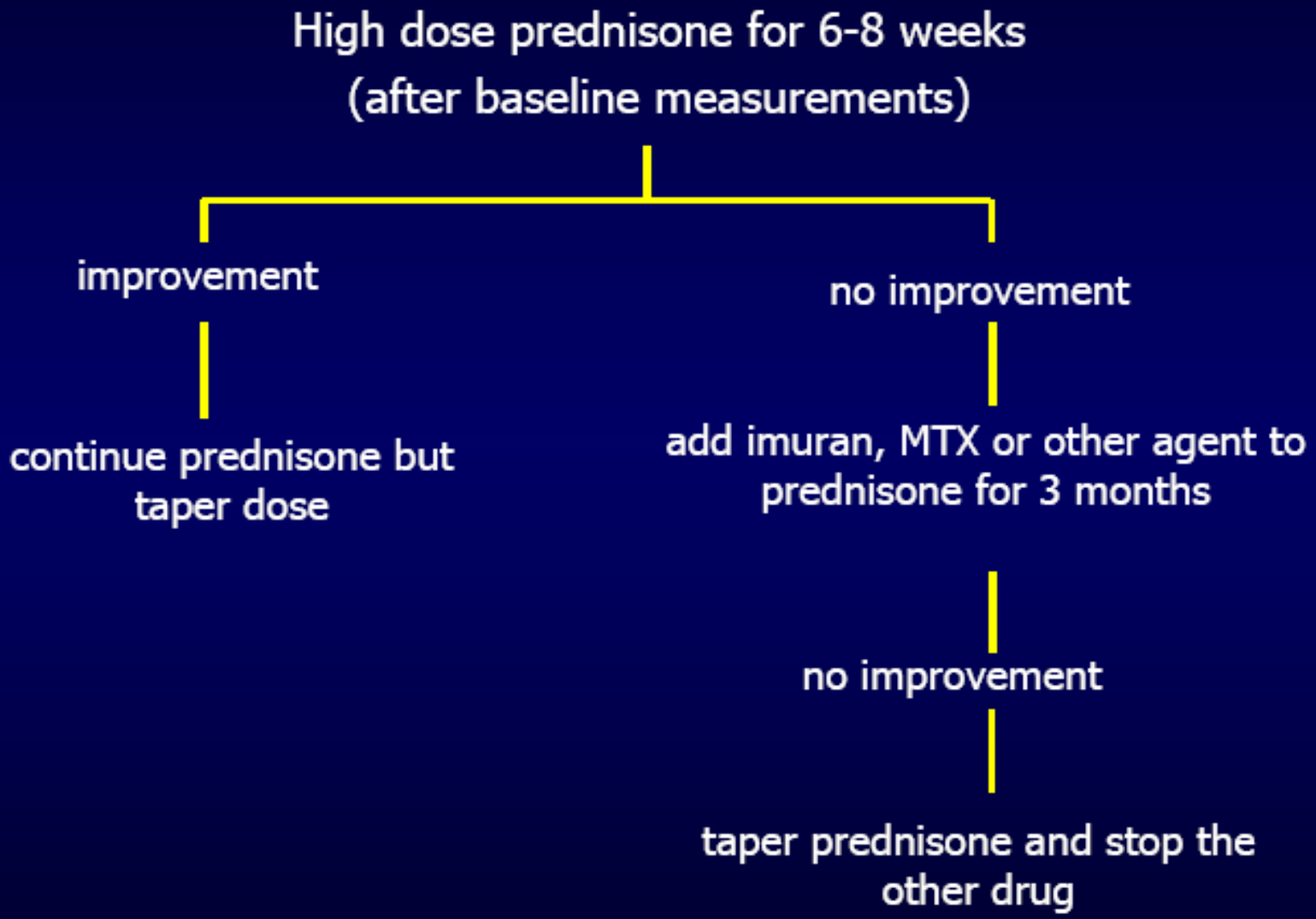



FrontalCortex.com

Differentiation between Inclusion Body Myositis and Polymyositis

	Inclusion body myositis	Polymyositis
Sex	Male>female	Female>male
Age	Rare before 50	Common before 50
Onset	Insidious	Acute or subacute
Course	Slowly progressive	More rapid
Distribution of weakness	Variable, may be primarily distal	Proximal, symmetric
Creatine kinase	Normal of <10x normal	Often >10x normal
EMG	Myopathic or mixed myopathic and neurogenic	Myopathic
Muscle biopsy	Inflammation, rimmed vacuoles, inclusions	Inflammation, fiber necrosis
Response to therapy	Generally poor	Expected

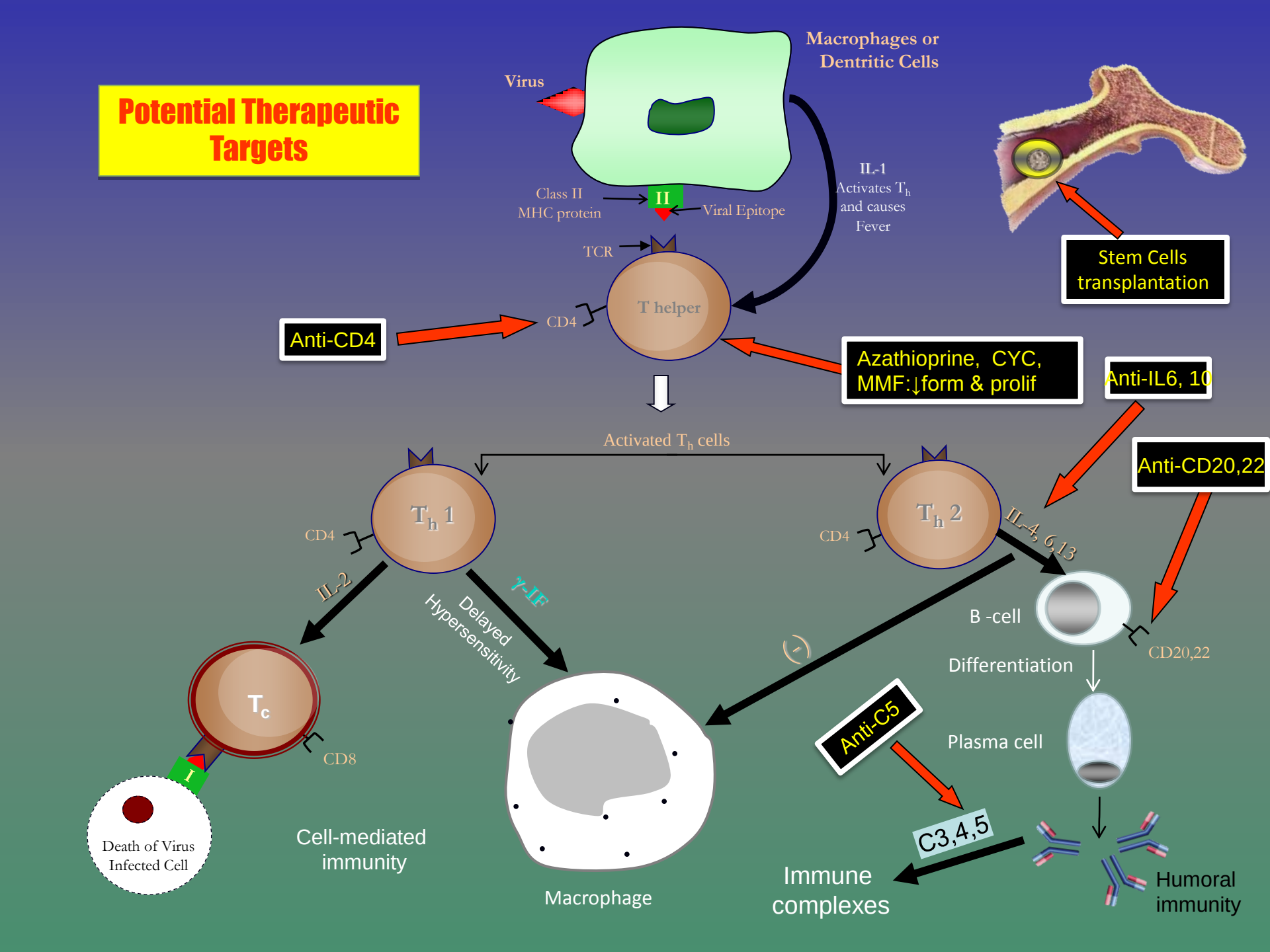
Approach to IBM Therapy



Inclusion Body Myositis

- Other treatments
- Specialized exercise therapy
- Teaching gait training with assistive devices, transfer and bed mobility
- Bimgrumab: still for approval

Thank You


Potential Therapeutic Targets
Macrophages or Dentritic Cells
Virus
Class II MHC protein
II
Viral Epitope
IL-1 Activates T_h and causes Fever
TCR
CD4
T helper
Anti-CD4
Azathioprine, CYC, MMF: ↓form & prolif
Stem Cells transplantation
Anti-IL6, 10
Anti-CD20,22
Activated T_h cells
T_h 1
T_h 2
CD4
IL-2
γ-IF
Delayed Hypersensitivity
IL-4, 6,13
B -cell
CD20,22
Differentiation
Plasma cell
T_c
CD8
I
Death of Virus Infected Cell
Cell-mediated immunity
Macrophage
Anti-C5
C3,4,5
Immune complexes
Humoral immunity

What type of myopathy is associated with statin therapy?

- The HMG-CoA reductase inhibitors (statins) can cause myalgias & cramps with or without a mildly elevated CK level in 1/10,000 individuals on low doses of statins and up to 1% of individuals on high doses.
- A small % of pts can develop a severe PM that does not resolve with discontinuation of the statin and may require immunosuppressive therapy. These patients are characterized by having **anti-200/100 antibodies** that target HMG-CoA reductase.
- Muscle biopsies: muscle **necrosis *without* inflammation**.
- Patients prone to develop a statin myopathy appear to have a genetic variant (C allele) of the *SLCO1B1* gene on chromosome 12 which codes for a protein involved with the uptake of statins and other compounds into the liver. Up to 2% of the population have two copies of this variant allele which gives them a 15% risk of developing a statin myopathy since more statin is available for uptake by the muscle.
- Interestingly other lipid-lowering agents can also cause a necrotizing myopathy including fibric acid derivatives (gemfibrozil) and nicotinic acid.